The Medical Research of Spirulina

Compiled and edited by: Bob Capelli
Stephanie Keily
Gerald R. Cysewski, PhD

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Section Two: Medical Research on the Key Nutrients in Spirulina

Introduction

There has been an extensive amount of research on the species Arthrospira Platensis, more commonly known as "Spirulina." This research dates back decades and has been conducted at universities, at government sponsored research facilities, as well as by private researchers throughout the world.

Cyanotech Corporation* feels that it is important to have a library of this research available for interested persons; hence we have created this document. Below the reader will find selected research abstracts on the health benefits of Spirulina and some of the major nutrients contained within Spiruilna. It was not practical to include full studies due to the massive amount of literature available; in addition, it was not practical to include all available abstracts. Particularly in the case of some of Spirulina's key nutrients, there were hundreds of abstracts available, so a significant amount of editing was necessary in order to present a manageable document.

The abstracts are presented according to health benefit as noted in the table of contents. In the case of studies that focused on more than one health benefit, the study is categorized according to the primary area of research within the abstract. All of the studies contained in this document are published and most can be found at www.pubmed.com

Any questions may be directed to Cyanotech Corporation, Kailua-Kona, Hawaii, USA, by e-mail at info@cyanotech.com or by telephone at 808.326.1353.

- Cyanotech Corporation is the producer of Hawaiian Spirulina Pacifica™ since 1984. Hawaiian Spirulina Pacifica is widely regarded as the world's highest quality Spirulina, with far superior levels of key nutrients than all other Spirulina products.

Antioxidant Research

Food Chem Toxicol. 2007 Dec;45(12):2412-9. Epub 2007 Jun 28.

Spirulina fusiformis provides protection against mercuric chloride induced oxidative stress in Swiss albino mice.

Sharma MK, Sharma A, Kumar A, Kumar M.

Department of Zoology, RLS Government (PG) College, Kaladera, Jaipur 303801, India. mkshrma@hotmail.com

Oxidative stress induced by mercuric chloride (5 mg/kg body weight i.p.) in mice substantially increases the lipid peroxidation level along with corresponding decrease in the reduced glutathione and various antioxidant enzymes in liver and increase in serum transaminases activity. Supplementation of Spirulina (800 mg/kg body weight orally, in olive oil, along with mercuric chloride) for 40 days resulted in decreased LPO level, serum glutamate oxaloacetate and serum glutamate pyruvate transaminase activity along with increase in liver GSH level. The activities of antioxidants enzymes superoxide dismutase, catalase and glutathione-S-transferase were also concomitantly restored to near normal level by Spirulina supplementation to mercuric chloride intoxicated mice. The results clearly demonstrate that Spirulina treatment augments the antioxidants defense mechanism in mercuric chloride induced toxicity and provides evidence that it may have a therapeutic role in free radical mediated diseases.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17706852 [PubMed - indexed for MEDLINE]

Biochem Biophys Res Commun. 2000 Aug 18;275(1):20-5.

C-phycocyanin: a potent peroxyl radical scavenger in vivo and in vitro.

Bhat VB, **Madyastha KM**.

Department of Organic Chemistry, Indian Institute of Science, Bangalore, 560 012, India.

C-Phycocyanin (from Spirulina platensis) effectively inhibited CCl(4)-induced lipid peroxidation in rat liver in vivo. Both native and reduced phycocyanin significantly inhibited peroxyl radical-induced lipid peroxidation in rat liver microsomes and the inhibition was concentration dependent with an IC(50) of 11.35 and 12.7 microM, respectively. The radical scavenging property of phycocyanin was established by studying its reactivity with peroxyl and hydroxyl radicals and also by competition kinetics of crocin bleaching. These studies have demonstrated that phycocyanin is a potent peroxyl radical scavenger with an IC(50) of 5.0 microM and the rate constant ratios obtained for phycocyanin and uric acid (a known peroxyl radical scavenger) were 1.54 and 3.5, respectively. These studies clearly suggest that the covalently linked chromophore, phycocyanobilin, is involved in the antioxidant and radical scavenging activity of phycocyanin.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 10944434 [PubMed - indexed for MEDLINE]

Antioxidant

J Sep Sci. 2005 Jun;28(9-10):1031-8.

Characterization via liquid chromatography coupled to diode array detector and tandem mass spectrometry of supercritical fluid antioxidant extracts of Spirulina platensis microalga.

Mendiola JA, Marín FR, Hernández SF, Arredondo BO, Señoráns FJ, Ibañez E, Reglero G.

Sección de Ciencias de la Alimentación, Universidad Autónoma de Madrid, Ciudad Universitaria de Cantoblanco, 28049 Madrid, Spain.

Spirulina platensis microalga has been extracted on a pilot scale plant using supercritical fluid extraction (SFE) under various extraction conditions. The extraction yield and the antioxidant activity of the extracts were evaluated in order to select those extracts with both the highest antioxidant capacity and a good extraction yield. These extracts were characterized using LC coupled to diode array detection (DAD) and LC coupled to mass spectrometry (MS) with two different interfaces, atmospheric pressure chemical ionization (APCI) and electrospray (ESI) which allowed us to perform tandem MS by using an ion trap analyzer. The best extraction conditions were as follows: CO2 with 10% of modifier (ethanol) as extraction solvent, 55 degrees C (extraction temperature) and 220 bar (extraction pressure). Fractionation was achieved by cascade depressurization providing two extracts with different activity and chemical composition. Several compounds have been identified in the extracts, corresponding to different carotenoids previously identified in Spirulina platensis microalga along with chlorophyll a and some degradation products. Also, the structure of some phenolic compounds could be tentatively identified. The antioxidant activity of the extracts could be attributed to some of the above mentioned compounds.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16013830 [PubMed - indexed for MEDLINE]

Antioxidant

J Agric Food Chem. 2005 May 18;53(10):4207-12.

Antioxidant and antiproliferative activities of Spirulina and Chlorella water extracts.

Wu LC, Ho JA, Shieh MC, Lu IW.

Department of Applied Chemistry, National Chi-Nan University, Puli, Nantou, Taiwan. lw25@ncnu.edu.tw

Liver fibrosis is a chronic liver disease that will further develop to cirrhosis if severe damage continues to form. A potential treatment for liver fibrosis is to inhibit activated hepatic stellate cell (HSC) proliferation and, subsequently, to induce HSC apoptosis. It has been reported that antioxidants are able to inhibit the proliferation of HSCs. In this study, the aqueous extract of spirulina was chosen as the source of antioxidant to investigate the inhibitory effect on the proliferation of HSC. The growth inhibitory effects of aqueous spirulina and chlorella extract on human liver cancer cells, HepG2, were also studied and compared in pairs. Results indicated that the total phenol content of spirulina was almost five times greater than that of chlorella (6.86 +/- 0.58 vs 1.44 +/- 0.04 mg tannic acid equivalent/g of algae powder, respectively). The antioxidant activity of spirulina determined by the ABTS*+ method was higher than chlorella (EC50: 72.44 +/- 0.24 micromol of trolox equivalent/g of spirulina extract vs 56.09 +/- 1.99 micromol of trolox equivalent/g of chlorella extract). Results of DPPH* assay also showed a similar trend as the ABTS*+ assay (EC50: 19.39 +/- 0.65 micromol of ascorbic acid equivalent/g of spirulina extract vs 14.04 +/- 1.06 micromol of ascorbic acid equivalent/g of chlorella extract). The aqueous extracts of these two algae both showed antiproliferative effects on HSC and HepG2, but spirulina was a stronger inhibitor than chlorella. Annexin-V staining showed that aqueous extract of spirulina induced apoptosis of HSC after 12 h of treatment. In addition, the aqueous extract of spirulina triggered a cell cycle arrest of HSC at the G2/M phase.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 15884862 [PubMed - indexed for MEDLINE]

Antioxidant

J Chromatogr A. 2004 Aug 27;1047(2):195-203.

Pressurized liquid extracts from Spirulina platensis microalga. Determination of their antioxidant activity and preliminary analysis by micellar electrokinetic chromatography.

Herrero M, **Ibáñez E**, **Cifuentes A**, **Señoráns J**.

Instituto de Fermentaciones Industriales (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain.

In this work, different extracts from the microalga Spirulina platensis are obtained using pressurized liquid extraction (PLE) and four different solvents (hexane, light petroleum, ethanol and water). Different extraction temperatures (115 and 170 degrees C) were tested using extraction times ranging from 9 to 15 min. The antioxidant activity of the different extracts is determined by means of an in vitro assay using a free radical method. Moreover, a new and fast method is developed using micellar electrokinetic chromatography with diode array detection (MEKC-DAD) to provide a preliminary analysis on the composition of the extracts. This combined application (i.e., in vitro assays plus MEKC-DAD) allowed the fast characterization of the extracts based on their antioxidant activity and the UV-vis spectra of the different compounds found in the extracts. To our knowledge, this work shows for the first time the great possibilities of the combined use of PLE-in vitro assay-MEKC-DAD to investigate natural sources of antioxidants.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15460249 [PubMed - indexed for MEDLINE]

Antioxidant

J Neural Transm. 2007 Sep;114(9):1217-25. Epub 2007 May 26.

Effect of spirulina maxima on the haloperidol induced tardive dyskinesia and oxidative stress in rats.

Thaakur SR, **Jyothi B**.

Department of Pharmacology, School of Pharmaceutical Sciences, Sri Padmavathi Mahila Viswa Vidyalayam, Andhra Pradesh, India. drsanthrani@gmail.com

Haloperidol is a widely used neuroleptic drug for the treatment of acute and chronic psychosis. The use of haloperidol is limited by extrapyramidal movement disorders such as Parkinsonism, akathesia, dystonia, and tardive dyskinesia (TD). Treatment with haloperidol increases oxyradicals which are implicated in TD. Spirulina is widely used as nutritional supplement rich in proteins and antioxidants. The present study is proposed to study the effect of spirulina on haloperidol induced TD and oxidative stress by studying TD, various enzymatic and nonenzymatic antioxidants and lipid peroxidation. Haloperidol 1 mg/kg/i.p was used to induce vacuous chewing movements in rats. Spirulina maxima suspended in 1% between 80 at a dose of 45, 90 and 180 mg/kg were administered by gavage along with haloperidol from 21st day to 49th day of treatment. Spirulina supplementation at a dose of 180 mg/kg significantly improved enzymatic and nonenzymatic antioxidants and decreased the tardive dyskinesia induced by haloperidol. In conclusion, the results of present investigation suggest that spirulina decreases haloperidol induced oxidative stress and TD by many mechanisms as it is cocktail of antioxidants. On chronic use it may inhibit haloperidol induced reduced expression of DNA thereby increases the expression of enzymatic and nonenzymatic antioxidants and protects against oxidative stress induced neurodegeneration and TD.

PMID: 17530160 [PubMed - in process]

Antioxidant

Indian J Biochem Biophys. 2006 Feb;43(1):25-31.

Antioxidant potential of C-phycocyanin isolated from cyanobacterial species Lyngbya, Phormidium and Spirulina spp.

Patel A, **Mishra S**, **Ghosh PK**.

Central Salt and Marine Chemicals Research Institute, GB Marg, Bhavnagar, India.

The antioxidant activity of C-Phycocyanin (C-PC) isolated from three cyanobacterial species Lyngbya (marine), Phormidium (marine) and Spirulina (fresh water) was studied in vitro. The results demonstrate that C-PCs from Lyngbya, Phormidium and Spirulina spp. are able to scavenge peroxyl radicals (determined by crocin bleaching assay) with relative rate constant ratio of 3.13, 1.89 and 1.8, respectively. C-PCs also scavenge hydroxyl radicals (determined by deoxyribose degradation assay) with second order rate constant values of 7.87 x 10(10), 9.58 x 10(10) and 6.42 x 10(10), respectively. Interestingly, Lyngbya C-PC is found to be an effective inhibitor of peroxyl radicals (IC50 6.63 microM), as compared to Spirulina (IC50 12.15 microM) and Phormidium C-PC (IC50 12.74 microM) and is close to uric acid (IC50 2.15 microM). Further, the studies suggest that the covalently-linked tetrapyrrole chromophore phycocyanobilin is involved in the radical scavenging activity of C-PC. The electron spin resonance (ESR) spectra of C-PCs indicate the presence of free radical active sites, which may play an important role in its radical scavenging property. This is the first report on the ESR activity of native C-PCs without perturbations that can cause radical formation.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16955748 [PubMed - indexed for MEDLINE]

J Appl Microbiol. 2009 Apr;106(4):1093-100. Epub 2009 Feb 23.

A potent anti-oxidant property: fluorescent recombinant alpha-phycocyanin of Spirulina.

Guan XY, Zhang WJ, Zhang XW, Li YX, Wang JF, Lin HZ, Tang XX, Qin S.

Ocean University of China, Qingdao, China.

AIMS: To express and product a fluorescent antioxidant holo-alpha-phycocyanin (PC) of Spirulina platensis (Sp) with His-tag (rHHPC; recombinant holo-alpha-phycocyaninof Spirulina platensis with His-tag) in 5-l bench scale. METHODS AND RESULTS: A vector harbouring two cassettes was constructed: cpcA along with cpcE-cpcF in one cassette; ho1-pcyA in the other cassette. Lyases CpcE/F of Synechocystis sp. PCC6803 (S6) could catalyse the 82 site Cys in apo-alpha-PC of Sp linking with bilin chromophores, and rHHPC was biosynthesized in Escherichia coli BL21. The constant feeding mode was adopted, and transformant reached the biomass of rHHPC up to 0.55 g l(-1) broth in 5-litre bench scale. rHHPC was purified by Ni(2+) affinity column conveniently. The absorbance and the fluorescence emission spectra of rHHPC had lambda(max) at 621 and 650 nm, respectively. The IC(50) values of rHHPC were 277.5 +/- 25.8 microg ml(-1) against hydroxyl radicals and 20.8 +/- 2.2 microg ml(-1) against peroxyl radicals. CONCLUSIONS: Combinational biosynthesis of rHHPC was feasible, and the constant feeding mode was adopted to produce good yields of rHHPC. Fluorescent rHHPC with several unique qualitative and quantitative features was effective on scavenging hydroxyl and peroxyl radicals. SIGNIFICANCE AND IMPACT OF THE STUDY: A potent antioxidant rHHPC was co-expressed, produced and characterized for nutritional and pharmacological values, which would help to develop phycobiliproteins' applications in their fluorescent and biological activities.

PMID: 19239531 [PubMed - in process]

Antioxidant

Phytother Res. 2008 May;22(5):627-33.

Antioxidant potential of selected Spirulina platensis preparations.

Dartsch PC.

Dartsch Scientific GmbH, Institut für zellbiologische Testsysteme, Horb am Neckar, Germany. pc.dartsch@dartsch-scientific.com

Recent studies suggest that Spirulina, a unicellular blue-green alga, may have a variety of health benefits and therapeutic properties and is also capable of acting as an antioxidant and antiinflammatory agent. In this study, a cell-free and a cell-based test assay were used to examine the antioxidant and antiinflammatory properties of four selected Spirulina platensis preparations: (1) Biospirulina, (2) SpiruComplex, a preparation with naturally bound selenium, chromium and zinc, (3) SpiruZink, a preparation with naturally bound zinc, (4) Zinkspirulina + Acerola, a preparation with naturally bound zinc and acerola powder. The cell-free test assay used potassium superoxide as a donor for superoxide radicals, whereas the cell-based test assay used the formation of intracellular superoxide radicals of functional neutrophils upon stimulation by phorbol-12-myristate-13-acetate as a model to investigate the potential of Spirulina preparations to inactivate superoxide radicals. In accordance with the recommended daily dosage, test concentrations ranging from 50 to 1000 microg/mL were chosen. The results showed a dose-dependent inactivation of free superoxide radicals (antioxidant effect) as well as an antiinflammatory effect characterized by a dose-dependent reduction of the metabolic activity of functional neutrophils and a dose-dependent inactivation of superoxide radicals generated during an oxidative burst. The results demonstrate that the tested Spirulina preparations have a high antioxidant and antiinflammatory potential. Especially SpiruZink and Zinkspirulina + Acerola might be useful as a supportive therapeutic approach for reducing oxidative stress and/or the generation of oxygen radicals in the course of inflammatory processes.

PMID: 18398928 [PubMed - indexed for MEDLINE]

Acta Pol Pharm. 2007 Jul-Aug;64(4):335-44.

In vitro evaluation of protective effects of ascorbic acid and water extract of Spirulina plantesis (blue green algae) on 5-fluorouracil-induced lipid peroxidation.

Ray S, **Roy K**, **Sengupta C**.

Division of Pharmaceutical Chemistry, Himalayan Pharmacy Institute, Majhitar, Rangpo, East Sikkim, 737 136, India. supratimray_in@yahoo.co.in

Considering drug-induced lipid peroxidation as a possible mediator of drug-induced toxicity and exploiting the free radical scavenging action of antioxidants, the present study was designed to evaluate the protective effects of ascorbic acid (AA) and water extract of Spirulina plantesis (SP) to minimize 5-fluorouracil (5-FU)-induced lipid peroxidation. The study has been performed in vitro using goat liver as an experimental model. This evaluation was done by measuring the malondialdehyde (MDA), reduced glutathione (GSH), 4-hydroxy-2-nonenal (4-HNE) and nitric oxide (NO) content of the tissue as markers of lipid peroxidation. The results suggest that ascorbic acid and water extract of Spirulina plantesis could suppress the 5-FU-induced lipid peroxidation to a significant extent.

Publication Types:

- In Vitro

PMID: 18536159 [PubMed - indexed for MEDLINE]

Anti-Inflammatory

J Med Food. 2007 Dec;10(4):566-70.

Clinical potential of Spirulina as a source of phycocyanobilin.

McCarty MF.

NutriGuard Research, Encinitas, CA 92024, USA. mccarty@pantox.com

Recent research reveals that free bilirubin functions physiologically as a potent inhibitor of NADPH oxidase activity. The chromophore phycocyanobilin (PCB), found in blue-green algae and cyanobacteria such as Spirulina, also has been found to be a potent inhibitor of this enzyme complex, likely because in mammalian cells it is rapidly reduced to phycocyanorubin, a close homolog of bilirubin. In light of the protean roles of NADPH oxidase activation in pathology, it thus appears likely that PCB supplementation may have versatile potential in prevention and therapy -- particularly in light of rodent studies demonstrating that orally administered Spirulina or phycocyanin (the Spirulina holoprotein that contains PCB) can exert a wide range of anti-inflammatory effects. Until PCB-enriched Spirulina extracts or synthetically produced PCB are commercially available, the most feasible and least expensive way to administer PCB is by ingestion of whole Spirulina. A heaping tablespoon (about 15 g) of Spirulina can be expected to provide about 100 mg of PCB. By extrapolating from rodent studies, it can be concluded that an intake of 2 heaping tablespoons daily would be likely to have important antioxidant activity in humans -- assuming that humans and rodents digest and absorb Spirulina-bound PCB in a comparable manner. An intake of this magnitude can be clinically feasible if Spirulina is incorporated into "smoothies" featuring such ingredients as soy milk, fruit juices, and whole fruits. Such a regimen should be evaluated in clinical syndromes characterized and in part mediated by NADPH oxidase overactivity in affected tissues.

Publication Types:

- Review

PMID: 18158824 [PubMed - indexed for MEDLINE]

Anesth Analg. 2009 Apr;108(4):1303-10.

Antiinflammatory and antihyperalgesic activity of C-phycocyanin.

Shih CM, **Cheng SN**, **Wong CS**, **Kuo YL**, **Chou TC**.

Chia-Yi Christian Hospital, Taipei, Taiwan, Republic of China.

BACKGROUND: C-phycocyanin (C-PC), a biliprotein found in blue green algae, such as Spirulina platensis, is often used as a dietary nutritional supplement due to its various therapeutic values. In addition, the antiinflammatory activity of C-PC partly through inhibition of proinflammatory cytokine formation, inducible nitric oxide synthase (iNOS) and cyclooxygeanase-2 (COX-2) expression has been demonstrated in many in vitro and in vivo studies. However, whether C-PC also has antihyperalgesic activity in inflammatory nociception has not been investigated. METHODS: Using a carrageenan-induced thermal hyperalgesia model, we evaluated the effect of C-PC on nociception by measuring paw withdrawal latency. To clarify the mechanisms involved, the expression of iNOS and COX-2 and the formation of nitrate and tumor necrosis factor-alpha (TNF-alpha) in the rat paw were determined. RESULTS: Pre- or posttreatment with C-PC (30 or 50 mg/kg, IP) significantly attenuated carrageenan-induced inflammatory nociception and the induction of iNOS and COX-2 at the late phase, (4 h) accompanied by an inhibition of the formation of TNF-alpha, prostaglandin E(2), nitrate and myeloperoxidase activity. CONCLUSIONS: Based on these results, it is suggested that the inhibition of NO and prostaglandin E(2) over-production through suppressing iNOS and COX-2 induction and attenuation of TNF-alpha formation and neutrophil infiltration into inflammatory sites by C-PC may contribute, at least in part, to its antihyperalgesic activity.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 19299804 [PubMed - indexed for MEDLINE]

Biochem Biophys Res Commun. 2000 Nov 2;277(3):599-603.

Selective inhibition of cyclooxygenase-2 by C-phycocyanin, a biliprotein from Spirulina platensis.

Reddy CM, **Bhat VB**, **Kiranmai G**, **Reddy MN**, **Reddanna P**, **Madyastha KM**.

Department of Organic Chemistry, Indian Institute of Science, Bangalore, 560 012, India.

We report data from two related assay systems (isolated enzyme assays and whole blood assays) that C-phycocyanin a biliprotein from Spirulina platensis is a selective inhibitor of cyclooxygenase-2 (COX-2) with a very low IC(50) COX-2/IC(50) COX-1 ratio (0.04). The extent of inhibition depends on the period of preincubation of phycocyanin with COX-2, but without any effect on the period of preincubation with COX-1. The IC(50) value obtained for the inhibition of COX-2 by phycocyanin is much lower (180 nM) as compared to those of celecoxib (255 nM) and rofecoxib (401 nM), the well-known selective COX-2 inhibitors. In the human whole blood assay, phycocyanin very efficiently inhibited COX-2 with an IC(50) value of 80 nM. Reduced phycocyanin and phycocyanobilin, the chromophore of phycocyanin are poor inhibitors of COX-2 without COX-2 selectivity. This suggests that apoprotein in phycocyanin plays a key role in the selective inhibition of COX-2. The present study points out that the hepatoprotective, anti-inflammatory, and anti-arthritic properties of phycocyanin reported in the literature may be due, in part, to its selective COX-2 inhibitory property, although its ability to efficiently scavenge free radicals and effectively inhibit lipid peroxidation may also be involved.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 11062000 [PubMed - indexed for MEDLINE]

Anti-Inflammatory

Arzneimittelforschung. 2000 Dec;50(12):1106-9.

Effects of phycocyanin extract on prostaglandin E2 levels in mouse ear inflammation test.

Romay C, **Ledón N**, **González R**.

Departamento de Farmacología, Centro Nacional de Investigaciones Científícas, CNIC, Habana, Cuba. Cheyla@quimica.cneuro.edu.cu

Recently it was demonstrated that phycocyanin, a biliprotein isolated from microalgae Spirulina, exerts anti-inflammatory activity in several animal models of inflammation. In this report, the effects of phycocyamin on prostaglandin E2 (PGE2) concentrations and phospholipase A2 (PLA2) activity were determined in arachidonic acid (AA) and 12-O-tetradecanoyl phorbol 13-acetate (TPA)-induced mouse ear oedema, respectively. Phycocyanin (50-200 mg/kg p.o.) inhibited in a dose-dependent manner PGE2 levels in mouse ear treated with AA. Also, phycocyanin (100-400 mg/kg p.o.) moderately reduced PLA2 activity in TPA-induced mouse ear inflammation test. In this model triamcinolone (10 mg/kg p.o.) used as reference drug exerted a remarkable inhibitory effect on PLA2 activity. These results provide the first evidence that the anti-inflammatory effects of phycocyanin may result, at least partially, from inhibition of PGE2 production and a moderate inhibition of PLA2 activity.

PMID: 11190776 [PubMed - indexed for MEDLINE]

Anti-Inflammatory

Mediators Inflamm. 2002 Apr;11(2):81-5.

Role of histamine in the inhibitory effects of phycocyanin in experimental models of allergic inflammatory response.

Remirez D, **Ledón N**, **González R**.

Ozone Research Center, National Center for Scientific Research, Havana, Cuba.

It has recently been reported that phycocyanin, a biliprotein found in the blue-green microalgae Spirulina, exerts anti-inflammatory effects in some animal models of inflammation. Taking into account these findings, we decided to elucidate whether phycocyanin might exert also inhibitory effects in the induced allergic inflammatory response and on histamine release from isolated rat mast cells. In in vivo experiments, phycocyanin (100, 200 and 300mg/kg post-orally (p.o.)) was administered 1 h before the challenge with 1 microg of ovalbumin (OA) in the ear of mice previously sensitized with OA. One hour later, myeloperoxidase activity and ear edema were assessed. Phycocyanin significantly reduced both parameters. In separate experiments, phycocyanin (100 and 200 mg/kg p.o.) also reduced the blue spot area induced by intradermal injections of histamine, and the histamine releaser compound 48/80 in rat skin. In concordance with the former results, phycocyanin also significantly reduced histamine release induced by compound 48/80 from isolated peritoneal rat mast cells. The inhibitory effects of phycocyanin were dose dependent. Taken together, our results suggest that inhibition of allergic inflammatory response by phycocyanin is mediated, at least in part, by inhibition of histamine release from mast cells.

PMID: 12061428 [PubMed - indexed for MEDLINE]

PMCID: PMC1781653

Mediators Inflamm. 2002 Apr;11(2):75-9.

Inhibitory effects of Spirulina in zymosan-induced arthritis in mice.

Remirez D, **González R**, **Merino N**, **Rodriguez S**, **Ancheta O**.

Ozone International Center, Havana, Cuba. ozono@infomed.sld.cu

The anti-inflammatory effect of microalgae Spirulina was studied in zymosan-induced arthritis in mice. Four days after the intra-articular injection of zymosan (15 mg/ml), Spirulina (100 and 400 mg/kg perorally) was administered to animals for 8 days. The mice were than killed and beta-glucuronidase was measured in the synovial fluid. Each knee joint was totally removed for histopathological studies. Spirulina significantly reduced the levels of beta-glucuronidase that had been increased by zymosan. Histopathological and ultrastructural studies showed inhibition of the inflammatory reaction, whereas no destruction of cartilage, well-preserved chondrocytes, and normal rough endoplasmic reticulum and mitochondria were seen. The anti-arthritic effect exerted by Spirulina as shown in this model may be at least partly due to the previously reported antiinflammatory and antioxidative properties of its constituent, phycocyanin. To our knowledge, this is the first report on the anti-inflammatory effect of Spirulina in an experimental model of arthritis.

PMID: 12061427 [PubMed - indexed for MEDLINE]

PMCID: PMC1781650

Biol Pharm Bull. 2006 Dec;29(12):2483-7.

Anti-inflammatory effect of Spirulina fusiformis on adjuvant-induced arthritis in mice.

Rasool M, **Sabina EP**, **Lavanya B**.

School of Bio-engineering and Biosciences, Vellore Institute of Technology, Deemed University, Tamilnadu, India. mkr474@rediffmail.com

The present study was carried out to evaluate the anti-inflammatory effect of Spirulina fusiformis on adjuvant-induced arthritis in mice. Arthritis was induced by intra dermal injection of complete freund's adjuvant (0.1 ml) into the right hind paw of Swiss albino mice. Spirulina fusiformis (800 mg/kg/b.wt) was orally administered for 8 d (from 11th to 18th day) to arthritic animals after adjuvant injection. The anti-inflammatory activity of Spirulina fusiformis was assessed by measuring paw volume, body weight, levels of lysosomal enzymes, tissue marker enzymes and glycoproteins in control and experimental animals. In adjuvant-induced arthritic animals, the levels of lysosomal enzymes, tissue marker enzymes, glycoproteins and the paw volume were increased significantly. However the body weight was found to be reduced when compared to control animals. Oral administration of Spirulina fusiformis (800 mg/kg/b.wt) significantly altered these above physical and biochemical changes observed in arthritic animals to near normal conditions. Hence results of this study clearly indicate that Spirulina fusiformis has promising anti-inflammatory activity against adjuvant-induced arthritic animals.

PMID: 17142986 [PubMed - indexed for MEDLINE]

Immunity

Zh Mikrobiol Epidemiol Immunobiol. 2001 Mar-Apr;(2):114-8.

[Biological activity of Spirulina]

[Article in Russian]

Blinkova LP, **Gorobets OB**, **Baturo AP**.

Mechnikov Research Institute for Vaccines and Sera, Moscow, Russia.

In this review information of Spirulina platensis (SP), a blue-green alga (photosynthesizing cyanobacterium) having diverse biological activity is presented. Due to high content of highly valuable proteins, indispensable amino acids, vitamins, beta-carotene and other pigments, mineral substances, indispensable fatty acids and polysaccharides, PS has been found suitable for use as bioactive additive. SP produces an immunostimulating effect by enhancing the resistance of humans, mammals, chickens and fish to infections, the capacity of influencing hemopoiesis, stimulating the production of antibodies and cytokines. Under the influence of SP macrophages, T and B cells are activated. SP sulfolipids have proved to be effective against HIV. Preparations obtained from SP biomass have also been found active against herpesvirus, cytomegalovirus, influenza virus, etc. SP extracts are capable in inhibiting cancerogenesis. SP preparations are regarded as functional products contributing to the preservation of the resident intestinal microflora, especially lactic acid bacilli and bifidobacteria, and to a decrease in the level of Candida albicans. The biological activity of SP with respect to microorganisms holds good promise for using these microalgae as components of culture media.

Publication Types:

- English Abstract
- Review

PMID: 11548244 [PubMed - indexed for MEDLINE]

Int Immunopharmacol. 2002 Mar;2(4):423-34.

Activation of the human innate immune system by Spirulina: augmentation of interferon production and NK cytotoxicity by oral administration of hot water extract of Spirulina platensis.

Hirahashi T, **Matsumoto M**, **Hazeki K**, **Saeki Y**, **Ui M**, **Seya T**.

Department of Immunology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan.

Spirulina platensis is a cyanobacterial species that is surmised to potentiate the immune system leading to suppression of cancer development and viral infection. Here, we identified the molecular mechanism of the human immune potentiating capacity of Spirulina by analyzing blood cells of volunteers with pre and post oral administration of hot water extract of Spirulina. NK functions represented by IFN gamma production and cytolysis were enhanced after administration of Spirulina in >50% subjects. IFN gamma was produced in an IL-12/IL-18-dependent fashion. In vitro stimulation of blood cells with BCG cell wall skeleton (CWS) allowed more potent IL-12 p40 production in cells from volunteers given Spirulina than in cells without pre-exposure to Spirulina. As BCG-CWS serves as a ligand for Toll-like receptor (TLR) 2 and 4 to raise the maturation stage of monocytes/macrophages, Spirulina may be involved in the signaling responses through Toll in blood cells even when orally administered. These observations indicated that in humans Spirulina acts directly on myeloid lineages and either directly or indirectly on NK cells. The presence of co-operative IL-12 and IL-18 is critically important for NK-mediated IFN gamma production.

Publication Types:

- Clinical Trial
- Research Support, Non-U.S. Gov't

PMID: 11962722 [PubMed - indexed for MEDLINE]

J Med Food. 2008 Jun;11(2):313-22.

Enhancement of human adaptive immune responses by administration of a high-molecular-weight polysaccharide extract from the cyanobacterium Arthrospira platensis.

Løbner M, Walsted A, Larsen R, Bendtzen K, Nielsen CH.

Department of Clinical Immunology and Blood Bank, Herlev Hospital, University of Copenhagen, Herlev, Denmark. mortenlobner@hotmail.com

The effect of consumption of Immulina, a high-molecular-weight polysaccharide extract from the cyanobacterium Arthrospira platensis, on adaptive immune responses was investigated by evaluation of changes in leukocyte responsiveness to two foreign recall antigens, Candida albicans (CA) and tetanus toxoid (TT), in vitro. Consumption of Immulina by 11 healthy male volunteers caused an immediate, but temporary, increase of CA-induced CD4+ T-helper (Th) cell proliferation ($P < .02$). TT-induced Th cell proliferation was increased in individuals over 50 years of age ($P < .05$) and correlated with age ($P < .02$). Consumption for 8 days enhanced the CA-induced B cell proliferation ($P < .02$), but after 56 days a diminution was seen ($P < .03$). The CA-elicited production of the Th1 cytokines tumor necrosis factor (TNF)-alpha, interleukin (IL)-2, and interferon (IFN)-gamma was increased after Immunlina administration for 3 days ($P < .001$, $< .03$, and $< .007$, respectively), and increased IL-2 production persisted after 56 days ($P < .004$). The TNF-alpha, IFN-gamma, and IL-6 responses to TT were enhanced after 8 and 14 days ($P < .002$-$.05$), while IL-5 responses increased significantly within 3 days ($P < .04$) and fell below baseline levels after 14 days ($P < .008$). Conversely, consumption for 3 days inhibited the IL-4 responses to both CA and TT ($P < .008$ and $P < .03$, respectively). No effects on IL-10 responses were observed. Upon addition to normal mononuclear cells in vitro, Immulina elicited strong TNF-alpha, IL-1beta, and IL-6 responses, indicating that it acts by inducing a pro-inflammatory state. Taken together, the data suggest that Immulina causes an age-dependent, temporary enhancement of adaptive immune responses.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18598175 [PubMed - indexed for MEDLINE]

J Nutr Sci Vitaminol (Tokyo). 2004 Apr;50(2):129-36.

Phycocyanin enhances secretary IgA antibody response and suppresses allergic IgE antibody response in mice immunized with antigen-entrapped biodegradable microparticles.

Nemoto-Kawamura C, Hirahashi T, Nagai T, Yamada H, Katoh T, Hayashi O.

Department of Health and Nutrition, Kagawa Nutrition University, Chiyoda, Sakado, Saitama 350-0288, Japan.

In the present study, we have investigated the effects of phycocyanin, a biliprotein of Spirulina platensis, on mucosal and systemic immune responses and allergic inflammation in C3H/HeN and BALB/cA mice. To induce the antigen-specific antibodies in the peripheral lymphoid tissues such as Peyer's patches and mesenteric lymph nodes, biodegradable ovalbumin-entrapped poly (DL-lactide-co-glycolide) particles were used as an antigen. Two weeks after the onset of phycocyanin ingestion, mice were immunized with an aqueous ovalbumin (OVA) solution. Starting at one week after the primary immunization, the mice were subjected to oral immunization with the biodegradable OVA microparticles twice a week. IgA, IgE and IgG1 antibodies were determined by ELISA. The OVA microparticles of 4-microm diameter successfully induced antigen-specific antibodies. In the mice that received phycocyanin treatment for 6 wk, a marked increase in the antigen-specific, as well as the total, IgA antibody level was observed in the Peyer's patches, mesenteric lymph nodes and intestinal mucosa as well as in the spleen cells. Both antigen-specific IgG1 and IgE antibody levels in the serum were suppressed by ingestion of phycocyanin for 8 wk. However, inflammation of the small intestine, monitored as vascular permeability by the Evans blue-leaking method was reduced by phycocyanin at 6 wk, which preceded the suppression of antigen-specific IgG1 and IgE antibody production by 2 wk. These results suggest that phycocyanin enhances biological defense activity against infectious diseases through sustaining functions of the mucosal immune system and reduces allergic inflammation by the suppression of antigen-specific IgE antibody.

PMID: 15242017 [PubMed - indexed for MEDLINE]

Arch Biochem Biophys. 2007 Mar 15;459(2):169-77. Epub 2007 Jan 29.

C-Phycocyanin inhibits 2-acetylaminofluorene-induced expression of MDR1 in mouse macrophage cells: ROS mediated pathway determined via combination of experimental and In silico analysis.

Roy KR, **Arunasree KM**, **Dhoot A**, **Aparna R**, **Reddy GV**, **Vali S**, **Reddanna P**.

Department of Animal Sciences, School of Life Sciences, University of Hyderabad, Hyderabad 500046, India.

We studied the effects of C-Phycocyanin (C-PC), a biliprotein from Spirulina platensis on the 2-acetylaminofluorene (2-AAF)-induced expression of MDR1, encoded by the multidrug resistance (MDR1) gene, in mouse macrophage cell line (RAW 264.7). Our experimental and In silico studies revealed a significant inhibition of 2-AAF-induced expression of MDR1 protein in C-PC treated mouse macrophage cell line. MDR1 induction by 2-AAF was dependent on ROS (reactive oxygen species)-Akt (protein kinase B)-NF-kappaB (Nuclear factor kappa B) signaling pathway. Generation of ROS, phosphorylation of Akt and corresponding nuclear translocation of NF-kappaB, the events that play a major role in the induction of MDR1 expression, were decreased significantly in C-PC treated cells. NADPH oxidase inhibitor, DPI (Diphenyl iodide), and pharmacological inhibitor of Akt, Akt inhibitor IV, also showed a reduction in MDR1 expression, although not to the same extent as C-PC mediated inhibition of MDR1 expression. To further understand the mechanism, we created a computational model of the detailed ROS-Akt-NF-kappaB pathway. C-PC was modeled purely as a ROS scavenger and this representation matched the experimental trends accurately. Also the ROS levels determined through In silico investigation showed that C-PC was more effective in reduction of MDR1 expression than inhibitors of NADPH oxidase and Akt. Our experimental and In silico studies collectively suggest that 2-AAF induces MDR1 by ROS dependent pathway and C-PC is a potential negative regulator of MDR1 expression. This down regulation of MDR1 expression, induced by xenobiotics such as 2-AAF, suggests C-PC's usefulness in overcoming the drug resistance in cellular systems.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17303067 [PubMed - indexed for MEDLINE]

Zh Mikrobiol Epidemiol Immunobiol. 1979 Dec;(12):75-9.

[Immunostimulating activity of the lipopolysaccharides of blue-green algae]

[Article in Russian]

Besednova NN, **Smolina TP**, **Mikheĭskaia LV**, **Ovodova RG**.

The whole cells of blue-gree algae and lipopolysaccharides isolated from these cells were shown to stimulate the production of macro-(mainly) and microglobulin antibodies in rabbits. The macro- and microphage indices in rabbits increased significantly after the injection of LPS isolated from blue-green algae 24--48 hours before infecting the animals with a virulent Y. pseudotuberculosis strain. Besides, the inhibiting action of this strain on the migration of phagocytes to the site of infection was abolished immediately after the injection. The use of the indirect hemagglutination test allowed to prove the absence of close antigenic interrelations between blue-green algae and the following organisms: Spirulina platensis, Microcystis aeruginosa, Phormidium africanum and P. uncinatum.

Publication Types:

- English Abstract

PMID: 117655 [PubMed - indexed for MEDLINE]

Vopr Pitan. 2006;75(2):19-21.

[Studies of immunomodulation caused by selenium-enriched phycocyanin]

[Article in Russian]

Egorova EA, **Gmoshinskiĭ IV**, **Zorin SN**, **Mazo VK**.

An influense was studied in rats of selenium enriched phycocyanin (Se-PC) from food microalgae Spirulina on anaphylactic reaction severity and circulating antibody response against model allergen--hen's egg white ovalbumin. Se-PC was introduced into diet in form of protein isolate precipitated with ammonia sulphate. Se-PC dosage made up to 450 mcg per rat daily that corresponded to 5 mcg of selenium. There were no differences revealed between experimental and control group that received standard diet in severity of anaphylactic reaction. Nevertheless rats receiving Se-PC demonstrated significantly increased specific IgG response. The probable immunomodulating properties of Se-PC included into food are discussed.

Publication Types:

- English Abstract

PMID: 16729754 [PubMed - indexed for MEDLINE]

Immunopharmacol Immunotoxicol. 2001 May;23(2):281-9.

Enhancement of chicken macrophage phagocytic function and nitrite production by dietary Spirulina platensis.

Al-Batshan HA, Al-Mufarrej SI, Al-Homaidan AA, Qureshi MA.

Department of Animal Production, College of Agriculture, King Saud University, Riyadh, Kingdom of Saudi Arabia.

The effects of dietary Spirulina platensis on chicken macrophage phagocytic function and nitrite production were examined. Day old broiler (meat-type) chicks were randomly assigned to various pens of electrically heated wire batteries. Dietary treatment groups included a basal diet with no dietary Spirulina added, and three additional groups with 0.5, 1.0 and 2.0% dietary Spirulina. Feed and water were provided for ad libitum consumption from one day of age. Sephadex-elicited macrophages were harvested at 14, 35 and 42 days of age. Phagocytosis assay was performed by co-incubating sheep red blood cells (SRBC) with the adherent macrophage monolayers. For nitrite quantification, macrophage cultures from various dietary treatment groups were stimulated in the presence or absence of 1 microg/mL of Escherichia coli lipopolysaccharide. These culture supernatant fractions were then tested for nitrite levels using the Greiss reagent technique. All Spirulina dietary group macrophages exhibited an enhanced phagocytic activity in terms of overall phagocytic percentage (range = 28 to 39% versus 24 to 25% in the basal group) and the average number of SRBC per phagocytic macrophage (range = 2.2 to 3.6 versus 1.8 to 2.5 in the basal group). This increase was linear with each incremental increase of dietary Spirulina. While LPS-induced nitrite levels in macrophages from basal diet group ranged from 60 to 278 microM over the three developmental ages, these levels in all Spirulina dietary groups were significantly higher (0.5% group range = 198 to 457 microM; 1.0% group range = 161 to 359 microM and 2.0% group range = 204 to 420 microM. These data clearly show that Spirulina platensis feeding upregulates macrophage phagocytic as well as metabolic pathways leading to increased nitric oxide synthase activity. These findings therefore imply that Spirulina platensis may enhance the functions of mononuclear phagocytic system thereby increasing the disease resistance potential in chickens.

Publication Types:

- In Vitro
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 11417854 [PubMed - indexed for MEDLINE]

Immunity

J Med Food. 2000 Fall;3(3):135-40.

Effect of spirulina on the secretion of cytokines from peripheral blood mononuclear cells.

Mao TK, VAN DE Water J, Gershwin ME.

ABSTRACT The purpose of this study was to evaluate the immunomodulatory activity of Spirulina, a bluegreen alga used as a food supplement. The effects of Spirulina on the secretion of three cytokines from unstimulated and stimulated human peripheral blood mononuclear cells (PBMC) were examined. In resting PBMC, Spirulina stimulated secretion of interleukin (IL)-1beta, IL-4, and interferon (IFN)-gamma to nearly 2.0, 3.3, and 13.6 times basal levels, respectively. Spirulina induced levels of IFN-gamma (229 +/- 104 pg/ml) that were comparable to those seen after phytohemagglutinin (PHA) stimulation (476 +/- 121 pg/ml). However, it was much less mitogenic than PHA (13.1 +/- 6.9 pg/ml) with respect to the induction of IL-4 secretion (0.34 +/- 0.1 pg/ml). In PHA-stimulated cells, Spirulina enhanced secretion of IL-1beta, IL-4, and IFN-beta by 2.9, 4.0., and 1.6 times, respectively. Although Spirulina stimulates several cytokines, it is clearly more effective in the generation of a Thl-type response. This in vitro study offers additional data for consideration of the potential therapeutic benefits of Spirulina.

PMID: 19281334 [PubMed - in process]

Lik Sprava. 2003 Jul-Aug;(5-6):102-5.

[Evaluation of the efficacy of a plant adaptogen (spirulina) in the pathognic therapy of primary tuberculosis in children]

[Article in Ukrainian]

Kostromina VP, **Derkach OV**, **Symonenkova NV**, **Riechkina OO**, **Otroshchenko AO**.

The use of spirulina and its efficiency have been studied in a comparative aspect as a systemic biocorrector, in a combined treatment of tuberculosis in 26 children. It has been ascertained that application of spirulina as a pathogenetic means of remediation permits shortening the intoxication syndrome regression time, reducing the frequency of adverse reactions in administering antituberculous preparations.

Publication Types:

- Clinical Trial
- Comparative Study
- English Abstract

PMID: 14618819 [PubMed - indexed for MEDLINE]

Planta Med. 2001 Nov;67(8):737-42.

Isolation of three high molecular weight polysaccharide preparations with potent immunostimulatory activity from Spirulina platensis, aphanizomenon flos-aquae and Chlorella pyrenoidosa.

Pugh N, **Ross SA**, **ElSohly HN**, **ElSohly MA**, **Pasco DS**.

Department of Pharmacognosy, School of Pharmacy, University of Mississippi, University, Mississippi 38677, USA.

This research describes the identification of three new high molecular weight polysaccharide preparations isolated from food-grade microalgae that are potent activators of human monocytes/macrophages: "Immulina" from Spirulina platensis, "Immunon" from Aphanizomenon flos-aquae, and "Immurella" from Chlorella pyrenoidosa. These polysaccharides are structurally complex and have estimated molecular weights above ten million daltons. All three polysaccharides are highly water soluble and comprise between 0.5 % and 2.0 % of microalgal dry weight.Immunostimulatory activity was measured using a transcription factor-based bioassay for nuclear factor kappa B (NF-kappa B) activation in THP-1 human monocytes/macrophages. Using this system the EC(50) values for these microalgal polysaccharides are between 20 and 110 ng/ml (about 10pM). THP-1 activation was confirmed by measuring immune cytokine mRNA induction using reverse transcriptase-polymerase chain reaction (RT-PCR). Each polysaccharide substantially increased mRNA levels of interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha). These polysaccharides are between one hundred and one thousand times more active for in vitro monocyte activation than polysaccharide preparations that are currently used clinically for cancer immunotherapy.

Publication Types:

- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 11731916 [PubMed - indexed for MEDLINE]

Biochim Biophys Acta. 1997 Mar 1;1355(3):241-7.

Calcium spirulan as an inducer of tissue-type plasminogen activator in human fetal lung fibroblasts.

Hayakawa Y, Hayashi T, Hayashi K, Ozawa T, Niiya K, Sakuragawa N.

Department of Clinical Laboratory Medicine, Faculty of Medicine, Toyama, Japan. hayakawa@ms.toyama-mpu.ac.jp

Calcium spirulan (Ca-SP), a novel sulfated polysaccharide isolated from the blue-green alga Spirulina platensis, has been found to have antiviral and heparin cofactor II-dependent antithrombin activities. We have obtained evidence that Ca-SP is a potent inducer of tissue-type plasminogen activator (t-PA) production. The addition of Ca-SP to a culture of IMR-90 human fetal lung fibroblasts increased t-PA concentrations in the conditioned medium, in a dose- and time-dependent manner, but in the cell lysate, t-PA concentrations were unchanged, suggesting that t-PA induced by Ca-SP is easily secreted into the conditioned medium. The amount of newly synthesized t-PA in IMR-90 cells, as measured by labeling with [35S]methionine and subsequent immunoprecipitation of t-PA from conditioned medium, was significantly increased by Ca-SP-stimulation. However, Ca-SP did not increase the t-PA mRNA levels. As previously reported, thrombin stimulated t-PA gene transcription in IMR-90 cells, and the simultaneous treatment with Ca-SP and thrombin caused further enhancement of t-PA production, in a synergistic manner. It would thus appear that Ca-SP increases t-PA production through post-transcriptional processes. IMR-90 cells also produce plasminogen activator inhibitor type-1 (PAI-1), but Ca-SP showed little effect on the PAI-1 production. H-SP, which was obtained by removing the calcium from Ca-SP, had no effect on the t-PA production. Na-SP, which was prepared by replacement of the calcium with sodium, stimulated the t-PA production similarly to Ca-SP. Thus, Ca-SP specifically induces t-PA production, and the molecular conformation of Ca-SP maintained by Ca or Na may be essential for the stimulation of t-PA synthesis.

PMID: 9060995 [PubMed - indexed for MEDLINE]

Immunopharmacol Immunotoxicol. 1996 Aug;18(3):465-76.

Dietary Spirulina platensis enhances humoral and cell-mediated immune functions in chickens.

Qureshi MA, Garlich JD, Kidd MT.

Department of Poultry Science, North Carolina State University, Raleigh 27695-7608, USA.

Cornell K-strain White Leghorns and broiler chicks were raised to 7 wks and 3 wks of age respectively, with diets containing various levels (0, 10, 100, 1,000 and 10,000 ppm) of Spirulina platensis from day of hatch. Chicks in all treatment groups had comparable body weights. While bursal and splenic weights did not change, the K-strain chicks had larger thymuses (P < or = .05) over the controls (0 ppm group). No differences were observed in anti-sheep red blood cells antibodies during primary response. However, during secondary response, K-strain chicks in all Spirulina-dietary groups had higher total anti-SRBC titers with 10,000 ppm group being the highest (6.8 Log2) versus the 0 ppm (5.5 Log2) group. In broiler chicks, a one Log increase in IgG (P < or = .05) was observed in 10,000 ppm group over the controls. Similarly, chicks in 10,000 ppm Spirulina group had a higher PHA-P-mediated lymphoproliferative response over the 0 ppm controls. Macrophages isolated from both K-strain (10,000 ppm group) and broilers from all Spirulina groups had higher phagocytic potential than the 0 ppm groups. Spirulina supplementation at 10,000 ppm level also increased NK-cell activity by two fold over the controls. These studies show that Spirulina supplementation increases several immunological functions implying that a dietary inclusion of Spirulina at a level of 10,000 ppm may enhance disease resistance potential in chickens.

PMID: 8872497 [PubMed - indexed for MEDLINE]

Immunopharmacol Immunotoxicol. 1996 Aug;18(3):457-63.

Spirulina platensis exposure enhances macrophage phagocytic function in cats.

Qureshi MA, **Ali RA**.

Department of Poultry Science, North Carolina State University, Raleigh 27695-7608, USA.

Bronchoalveolar lavage macrophages isolated from cats were cultured on glass coverslips. Macrophages were exposed to a water-soluble extract of Spirulina platensis in concentration range of 0 to 60 micrograms per mL for two hours. Spirulina-extract exposure did not cause significant macrophage cytotoxicity over untreated control cultures. Macrophage monolayers from treated and control cultures were incubated with sheep red blood cells (SRBC) as well as viable Escherichia coli. The percentages of phagocytic macrophages for both of these particulate antigens were higher (a two-fold increase in SRBC phagocytosis and over 10% increase in Escherichia coli uptake) in cultures treated with various concentrations of Spirulina-extract. However, the numbers of either types of particles internalized by phagocytic macrophage were not different between the control and treated cultures. These data which showed that Spirulina platensis extract enhances macrophage phagocytic function imply that dietary Spirulina supplementation may improve the disease resistance potential in cats.

PMID: 8872496 [PubMed - indexed for MEDLINE]

J Nutr Sci Vitaminol (Tokyo). 1994 Oct;40(5):431-41.

Enhancement of antibody production in mice by dietary Spirulina platensis.

Hayashi O, **Katoh T**, **Okuwaki Y**.

Department of Health and Nutrition, Kagawa Nutrition University, Sakado, Japan.

Mice fed a Spirulina platensis diet showed increased numbers of splenic antibody-producing cells in the primary immune response to sheep red blood cells (SRBC). However, immunoglobulin G (IgG)-antibody production in the secondary immune response was hardly affected. The percentage of phagocytic cells in peritoneal macrophages from the mice fed S. platensis diet, as well as the proliferation of spleen cells by either concanavalin A (Con A) or phytohemagglutinin (PHA) was significantly increased. Addition of a hot-water extract of S. platensis (SHW) to an in vitro culture of spleen cells markedly increased proliferation of these cells, whereas culture of thymus cells was scarcely affected. The Spirulina extract also significantly enhanced interleukin-1 (IL-1) production from peritoneal macrophages. Addition to the in vitro spleen cell culture of SHW as well as the supernatant of macrophages stimulated with SHW resulted in enhancement of antibody production, that is, an increase of the number of PFC. These results suggest that Spirulina enhances the immune response, particularly the primary response, by stimulating macrophage functions, phagocytosis, and IL-1 production.

PMID: 7891204 [PubMed - indexed for MEDLINE]

Phytother Res. 2004 Sep;18(9):754-7.

Antibacterial activity of volatile component and various extracts of Spirulina platensis.

Ozdemir G, Karabay NU, Dalay MC, Pazarbasi B.

Ege University, Faculty of Science, Department of Biology, 35100 Bornova, Izmir, Turkey. gozdemir@sci.ege.edu.tr

The methanol, dichloromethane, petroleum ether, ethyl acetate extracts and volatile components of Spirulina platensis were tested in vitro for their antimicrobial activity (four Gram-positive, six Gram-negative bacteria and Candida albicans ATCC 10239). GC-MS analysis of the volatile components of S. platensis resulted in the identification of 15 compounds which constituted 96.45% of the total compounds. The volatile components of S. platensis consisted of heptadecane (39.70%) and tetradecane (34.61%) as major components. The methanol extract showed more potent antimicrobial activity than dichloromethane, petroleum ether, ethyl acetate extracts and volatile components.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15478198 [PubMed - indexed for MEDLINE]

Vopr Pitan. 2007;76(2):21-5.

[The influence of Spirulina and Selen-Spirulina on some indexes of rat's immune status]

[Article in Russian]

Trushina EN, **Gladkikh O**, **Gadzhieva ZM**, **Mustafina OK**, **Pozdniakov AL**.

This paper reviews evidence for the immune-enhancing effect of Spirulina (Sp) and Selen-Spirulina (Se-Sp) in male Wistar rats. The rats of control group fed half-synthetic diet. Rats of experimental groups consumed the half-synthetic diets with Sp (10 g/kg diet) or Se-Sp (350 microg Se/kg diet) for 2 weeks. Using rats lymphocytes in vitro after phytohemagglutinin stimulation was demonstrated that lymphocytes from Sp and Se-Sp groups secreted of interleukin-2 and interferon-gamma more control group. Induction of interleukin-4 was comparable with once of control group. We believed that Sp and Se-Sp are more effective in stimulating a Th-1--type response and hence potentiates cell-mediated immunity. The immunostimulatory effect of Sp and Se-Sp was confirmed by morphologic and morphometric investigation of rats spleen, also with by NBT-test of peritoneal macrophages.

Publication Types:

- Comparative Study
- English Abstract

PMID: 17561650 [PubMed - indexed for MEDLINE]

Int Immunopharmacol. 2006 Dec 5;6(12):1808-14. Epub 2006 Aug 28.

Toll-like receptor 2-dependent activation of monocytes by Spirulina polysaccharide and its immune enhancing action in mice.

Balachandran P, **Pugh ND**, **Ma G**, **Pasco DS**.

National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677, USA.

We reported previously that a high molecular weight polysaccharide fraction (Immulina) from Spirulina was a potent activator of NF-kappa B and induced both IL-1 beta and TNF-alpha mRNAs in THP-1 human monocytes. In the present study, we show that NF-kappa B activation by Immulina is suppressed by antibodies to CD14 and TLR2 but not by antibodies to TLR4. Similarly, NF-kappa B directed luciferase expression was enhanced by Immulina treatment when cells were co-transfected with vectors expressing proteins supporting TLR2- (CD14 and TLR2) but not TLR4-(CD14, TLR4, and MD-2) dependent activation. Mice that consumed a chemically defined chow mixed with an extract containing Immulina exhibited changes in several immune parameters. The ex vivo production of IgA and IL-6 from Peyer's patch cells was enhanced 2-fold and interferon-gamma production from spleen cells was increased 4-fold in Immulina-treated mice. The enhanced production of these factors was most notable with mice that had consumed this extract for 4 or 5 days. These studies shed light on how Immulina activates cells of the innate immune system and suggests that oral consumption of this polysaccharide can enhance components within both the mucosal and systemic immune systems.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 17052671 [PubMed - indexed for MEDLINE]

J Altern Complement Med. 2006 Jun;12(5):429-35.

Immolina, a high-molecular-weight polysaccharide fraction of Spirulina, enhances chemokine expression in human monocytic THP-1 cells.

Grzanna R, Polotsky A, Phan PV, Pugh N, Pasco D, Frondoza CG.

RMG Biosciences, Inc., Baltimore, MD, USA.

INTRODUCTION: Spirulina (Spirulina platensis) is a dietary supplement valued for its immune-enhancing properties. We previously reported that the immunostimulatory effect of spirulina can be traced to a high-molecular- weight polysaccharide fraction. This fraction, labeled Immolina, activates nuclear factor kappa-B in human monocytic THP-1 cells and increases expression of proinflammatory cytokines. OBJECTIVE: To characterize further the immunostimulatory effects of Immolina on THP-1 cells, we evaluated its effect on genes encoding the chemokines interleukin (IL)-8, MCP-1, MIP-1alpha, MIP-1beta, IP-10, the cytokines tumor necrosis factor (TNF)-alpha, IL-1beta, and the enzyme cyclo-oxygenase-2 (COX-2). METHODS: THP-1 cells were exposed to concentrations of Immolina ranging from 1 ng/mL to 100 microg/mL and changes in gene expression were assessed by reverse transcriptase-polymerase chain reaction (RT-PCR). For comparison, THP-1 cells were activated with 1 ng/mL of TNF-alpha, 10 ng/mL of IL-1beta, or 10 ng/mL of lipopolysaccharide using the same assay conditions. To assess the response of THP-1 cells to Immolina at the protein level, we probed culture supernatants using a cytokine array immunoblot assay. RESULTS: RT-PCR analysis revealed that Immolina dose-dependently increased the expression of all 5 chemokines tested as well as the expression of TNF-alpha, IL-1beta, and COX-2. The cytokine array immunoblot assay revealed an increase in the chemokines IL-8 and MIP-1beta. Thymidine uptake experiments verified that Immolina did not affect the viability and growth rate of THP-1 cells. CONCLUSIONS: The results of the experiments demonstrate that Immolina activates THP-1 cells in a manner that is consistent with the recruitment of diverse populations of leukocytes in response to inflammatory and infectious signals.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 16813506 [PubMed - indexed for MEDLINE]

Immunity

Nat Med (Tokyo). 2009 Apr;63(2):169-75. Epub 2008 Dec 18.

Appraisal of immunomodulatory potential of Spirulina fusiformis: an in vivo and in vitro study.

Rasool M, **Sabina EP**.

Faculty of Heath and Life Sciences, Management and Science University, Sekysen 13, Shah Alam, Selangor Darul Ehsan, Malaysia. mkr474@gmail.com

In recent years, Spirulina has gained more and more attention from medical scientists as a nutraceutical and a source of potential pharmaceuticals. The present study was conducted to elucidate the immunomodulatory effect of Spirulina fusiformis (a cyanobacterium of the family Oscillatoriaceae) in vivo and in vitro. The in vivo effect of S. fusiformis (400 or 800 mg/kg body wt.) on humoral immune response, cell-mediated immune response and tumour necrosis factor alpha was investigated in mice. We also evaluated the effect of S. fusiformis (50 or 100 microg/ml) in vitro on mitogen (phytohaemagglutinin)-induced T lymphocyte proliferation in heparinized human peripheral blood. For comparison, dexamethasone was used as a standard. In mice, S. fusiformis (400 or 800 mg/kg body wt.) administration significantly inhibited the humoral immune response, cell-mediated immune response (delayed-type hypersensitivity reaction (DTH)) and tumour necrosis factor alpha in a dose-dependent manner. In vitro, S. fusiformis (50 or 100 microg/ml) decreased the mitogen (phytohaemagglutinin)-induced T lymphocyte proliferation in a concentration-dependent manner when compared with control cells. These observations clearly suggest that S. fusiformis has a remarkable immunosuppressive effect, which provides a scientific validation for the popular use of this drug, and helped us in further work on investigating its complete mechanism of action.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 19093070 [PubMed - indexed for MEDLINE]

Evid Based Complement Alternat Med. 2008 Sep 14. [Epub ahead of print]

Spirulina in Clinical Practice: Evidence-Based Human Applications.

Karkos PD, **Leong SC**, **Karkos CD**, **Sivaji N**, **Assimakopoulos DA**.

Specialist Registrar in Otolaryngology, 36 Hopkinsons Court, Walls Avenue, Chester CH1 4LN, UK. E- pkarkos@aol.com.

Spirulina or Arthrospira is a blue-green alga that became famous after it was successfully used by NASA as a dietary supplement for astronauts on space missions. It has the ability to modulate immune functions and exhibits anti-inflammatory properties by inhibiting the release of histamine by mast cells. Multiple studies investigating the efficacy and the potential clinical applications of Spirulina in treating several diseases have been performed and a few randomized controlled trials and systematic reviews suggest that this alga may improve several symptoms and may even have an anticancer, antiviral and antiallergic effects. Current and potential clinical applications, issues of safety, indications, side-effects and levels of evidence are addressed in this review. Areas of ongoing and future research are also discussed.

PMID: 18955364 [PubMed - as supplied by publisher]

Chemopreventative

Clin Exp Metastasis. 1998 Aug;16(6):541-50.

Inhibition of tumor invasion and metastasis by calcium spirulan (Ca-SP), a novel sulfated polysaccharide derived from a blue-green alga, Spirulina platensis.

Mishima T, Murata J, Toyoshima M, Fujii H, Nakajima M, Hayashi T, Kato T, Saiki I.

Research Institute for Wakan-Yaku, Toyama Medical and Pharmaceutical University, Japan.

We have investigated the effect of calcium spirulan (Ca-SP) isolated from a blue-green alga, Spirulina platensis, which is a sulfated polysaccharide chelating calcium and mainly composed of rhamnose, on invasion of B16-BL6 melanoma, Colon 26 M3.1 carcinoma and HT-1080 fibrosarcoma cells through reconstituted basement membrane (Matrigel). Ca-SP significantly inhibited the invasion of these tumor cells through Matrigel/fibronectin-coated filters. Ca-SP also inhibited the haptotactic migration of tumor cells to laminin, but it had no effect on that to fibronectin. Ca-SP prevented the adhesion of B16-BL6 cells to Matrigel and laminin substrates but did not affect the adhesion to fibronectin. The pretreatment of tumor cells with Ca-SP inhibited the adhesion to laminin, while the pretreatment of laminin substrates did not. Ca-SP had no effect on the production and activation of type IV collagenase in gelatin zymography. In contrast, Ca-SP significantly inhibited degradation of heparan sulfate by purified heparanase. The experimental lung metastasis was significantly reduced by co-injection of B16-BL6 cells with Ca-SP. Seven intermittent i.v. injections of 100 microg of Ca-SP caused a marked decrease of lung tumor colonization of B16-BL6 cells in a spontaneous lung metastasis model. These results suggest that Ca-SP, a novel sulfated polysaccharide, could reduce the lung metastasis of B16-BL6 melanoma cells, by inhibiting the tumor invasion of basement membrane probably through the prevention of the adhesion and migration of tumor cells to laminin substrate and of the heparanase activity.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9872601 [PubMed - indexed for MEDLINE]

Chemopreventative

Nutr Cancer. 1995;24(2):197-202.

Evaluation of chemoprevention of oral cancer with Spirulina fusiformis.

Mathew B, **Sankaranarayanan R**, **Nair PP**, **Varghese C**, **Somanathan T**, **Amma BP**, **Amma NS**, **Nair MK**.

Regional Cancer Centre, Medical College Campus, Kerala, India.

The blue-green microalgae Spirulina, used in daily diets of natives in Africa and America, have been found to be a rich natural source of proteins, carotenoids, and other micronutrients. Experimental studies in animal models have demonstrated an inhibitory effect of Spirulina algae on oral carcinogenesis. Studies among preschool children in India have demonstrated Spirulina fusiformis (SF) to be an effective source of dietary vitamin A. We evaluated the chemopreventive activity of SF (1 g/day for 12 mos) in reversing oral leukoplakia in pan tobacco chewers in Kerala, India. Complete regression of lesions was observed in 20 of 44 (45%) evaluable subjects supplemented with SF, as opposed to 3 of 43 (7%) in the placebo arm ($p < 0.0001$). When stratified by type of leukoplakia, the response was more pronounced in homogeneous lesions: complete regression was seen in 16 of 28 (57%) subjects with homogeneous leukoplakia, 2 of 8 with erythroplakia, 2 of 4 with verrucous leukoplakia, and 0 of 4 with ulcerated and nodular lesions. Within one year of discontinuing supplements, 9 of 20 (45%) complete responders with SF developed recurrent lesions. Supplementation with SF did not result in increased serum concentration of retinol or beta-carotene, nor was it associated with toxicity. This is the first human study evaluating the chemopreventive potential of SF. More studies in different settings and different populations are needed for further evaluation.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 8584455 [PubMed - indexed for MEDLINE]

Chemopreventative

Nutr Cancer. 1988;11(2):127-34.

Prevention of experimental oral cancer by extracts of Spirulina-Dunaliella algae.

Schwartz J, Shklar G, Reid S, Trickler D.

Department of Oral Medicine and Oral Pathology, Harvard School of Dental Medicine, Boston, MA 02115.

An extract of Spirulina-Dunaliella algae was shown to prevent tumor development in hamster buccal pouch when a 0.1% solution of 7,12-dimethylbenz[a]anthracene (DMBA) in mineral oil was applied topically three times weekly for 28 weeks. The algae extract was delivered by mouth in continued dosages of 140 micrograms in 0.4 ml mineral oil three times per week. After 28 weeks, the animals given vehicle and untreated controls all presented gross tumors of the right buccal pouch. Animals fed canthaxanthin presented a notably and statistically significant reduction in tumor number and size compared with controls. Animals fed beta-carotene demonstrated a smaller but statistically significant reduction in tumor number and size. The algae animals presented a complete absence of gross tumors. However, microscopic sections of the buccal pouch in the algae group showed localized areas of dysplasia and early carcinoma-in-situ undergoing destruction.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 3129701 [PubMed - indexed for MEDLINE]

Chemopreventative

Space Med Med Eng (Beijing). 2003;16 Suppl:514-8.

[Protective effect of natural dietary antioxidants on space radiation-induced damages]

[Article in Chinese]

Chen B, **Zhou XC**.

Institute of Space Medico-Engineering, Beijing, China.

This paper described the radiation-induced damage on human body in space and summarized the studies of antioxidants such as Vit C, Vit E, Vit A, beta-carotene, flavonoids, polysaccharide, green-tea and Spirulina protection against radiation-induced damage. Application prospects of natural antioxidants in space food were also put forward in this article.

Publication Types:

- English Abstract

PMID: 14989308 [PubMed - indexed for MEDLINE]

Chemopreventative

J Agric Food Chem. 2008 Jun 25;56(12):4352-8. Epub 2008 Jun 4.

In vitro antioxidant and antiproliferative activities of selenium-containing phycocyanin from selenium-enriched Spirulina platensis.

Chen T, **Wong YS**.

Research Laboratory for Food Protein Production and Food and Nutritional Sciences Programme, Department of Biology, The Chinese University of Hong Kong, Hong Kong SAR, China.

Both selenium and phycocyanin have been reported to show potent cancer chemopreventive activities. In this study, we investigated the in vitro antioxidant and antiproliferative activities of selenium-containing phycocyanin (Se-PC) purified from selenium-enriched Spirulina platensis. The antioxidant activity of Se-PC was evaluated by using four different free radical scavenging assays, namely, the 2,2'-azinobis-3-ethylbenzothiazolin-6-sulfonic acid (ABTS) assay, 1,1-diphenyl-2-picryhydrazyl (DPPH) assay, superoxide anion scavenging assay, and erythrocyte hemolysis assay. The results indicated that Se-PC exhibited stronger antioxidant activity than phycocyanin by scavenging ABTS, DPPH, superoxide anion, and 2,2'-azobis-(2-amidinopropane)dihydrochloride free radicals. Se-PC also showed dose-dependent protective effects on erythrocytes against H 2O 2-induced oxidative DNA damage as evaluated by the Comet assay. Moreover, Se-PC was identified as a potent antiproliferative agent against human melanoma A375 cells and human breast adenocarcinoma MCF-7 cells. Induction of apoptosis in both A375 and MCF-7 cells by Se-PC was evidenced by accumulation of sub-G1 cell populations, DNA fragmentation, and nuclear condensation. Further investigation on intracellular mechanisms indicated that depletion of mitochondrial membrane potential (DeltaPsi m) was involved in Se-PC-induced cell apoptosis. Our findings suggest that Se-PC is a promising organic Se species with potential applications in cancer chemoprevention.

PMID: 18522403 [PubMed - indexed for MEDLINE]

Chemopreventative

Radiats Biol Radioecol. 2000 May-Jun;40(3):310-4.

[The postradiation use of vitamin-containing complexes and a phycocyanin extract in a radiation lesion in rats]

[Article in Russian]

Karpov LM, **Brown II**, **Poltavtseva NV**, **Ershova ON**, **Karakis SG**, **Vasil'eva TV**, **Chaban IuL**.

Mechnikov Odessa State University, Ukraina.

Wistar rats have been exposed to X-rays with a dose of 5 Gy. Significant decrease in dehydrogenase activity, energy-rich phosphate level and efficiency of antioxidant defence and significant increase in pyruvate amount were observed within 4 weeks. It was also found that the feeding of exposed rats with phycocyanin extract from blue-green algae Spirulina platensis lead to correcting effect. The same result was observed after injections of tocopherol or complex of six water-soluble vitamins. The combination of above mentioned compounds had more marked effect, especially at the presence unitiole and Na2Se.

Publication Types:

- Comparative Study
- English Abstract

PMID: 10907410 [PubMed - indexed for MEDLINE]

Chemopreventative

Biotechnol Appl Biochem. 2006 Mar;43(Pt 3):155-64.

Molecular immune mechanism of C-phycocyanin from Spirulina platensis induces apoptosis in HeLa cells in vitro.

Li B, **Gao MH**, **Zhang XC**, **Chu XM**.

College of Marine Life Sciences, Ocean University of China, Qingdao 266003, People's Republic of China.

C-phycocyanin (C-PC), a water-soluble protein pigment, isolated from Spirulina platensis, is of great importance because of its various medical and pharmacological properties. In the present study, we first investigated the effect of highly purified C-PC on growth and proliferation of HeLa cells in vitro. The results indicated that there was a significant decrease in the number of cells that survived for HeLa cells treated with C-PC compared with control cells untreated with C-PC. Further electron-microscopic studies revealed that C-PC could induce characteristic apoptotic features, including cell shrinkage, membrane blebbing, microvilli loss, chromatin margination and condensation into dense granules or blocks. Agarose electrophoresis of genomic DNA of HeLa cells treated with C-PC showed fragmentation pattern (DNA ladder of oligomers of 180-200 bp) typical for apoptotic cells. Flow-cytometric analysis of HeLa cells treated with different concentrations of C-PC demonstrated an increasing percentage of cells in sub-G0/G1 phase. In addition, we found that C-PC could promote the expression of Fas and ICAM-1 (intercellular cell-adhesion molecule 1) protein, while it held back the Bcl-2 (B-cell lymphocytic-leukaemia proto-oncogene 2) protein expression. This suggested that C-PC could induce the activation of pro-apoptotic gene and downregulation of anti-apoptotic gene expression and then facilitate the transduction of tumoural apoptosis signals that resulted in the apoptosis of HeLa cells in vitro. Caspases 2, 3, 4, 6, 8, 9, and 10 were activated in C-PC-treated HeLa cells, which suggested that C-PC-induced apoptosis was caspase-dependent. C-PC treatment of HeLa cells also resulted in release of cytochrome c from the mitochondria into the cytosol that was related to apoptosis of C-PC-treated HeLa cells.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16316316 [PubMed - indexed for MEDLINE]

Chemopreventative

Biomed Pharmacother. 2005 Dec;59(10):551-60. Epub 2005 Oct 25.

Effects of CD59 on antitumoral activities of phycocyanin from Spirulina platensis.

Li B, **Zhang X**, **Gao M**, **Chu X**.

Department of Marine Biology, Institution of Life Science and Technology, Ocean University of China, 5 Yushan Road, Qingdao 266003, China.

The regulatory effect of phycocyanin (PC) from Spirulina platensis on cluster of differentiation 59 (CD59) gene expression of Hela cells and antitumoral mechanism of PC was investigated in this study. PC was purified by hydroxylapatite (HA) and sephacrylHR-200 gel-filtration columns chromatography. The molecular weight of PC was determined by SDS-PAGE electrophoresis. The CD59 cDNA was inserted into the eukaryotic expression plasmid pALTER-MAX, and the recombinant vector pALTER-MAX-CD59 was successfully constructed. By using cationic liposome (Lipfectamine-2000)-mediated transfection method, the recombinant plasmid pALTER-MAX-CD59 and the selective marker PcDNA were cotransfected into Hela cells and normal Chinese hamster ovary (CHO) cells. Stable positive cell clones were sorted out and disposed with different concentrates of PC. The expression of CD59 protein was determined by in situ hybridization, immunofluorescence and enzyme linked immunosorbent assay (ELISA). In addition, the effect of PC on the proliferation of Hela cells was determined by MTT method and the expression of Fas protein was by immunohistochemistry. Results showed that PC can promote the expression of CD59 protein in Hela cells, hold back it is reproductions of Hela cells, and moreover, a dosage effect was found between them. Namely, with the ascendance of PC concentration, the expression quantities of CD59 protein and apoptosis-inducing Fas protein increased and the multiplication activity of Hela cells declined, whereas PC was of no use to CD59 and Fas protein expression, and reproduction of normal CHO cells as well. Besides an imaginable antitumoral molecular immune mechanism of PC was brought forward and discussed.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 16271846 [PubMed - indexed for MEDLINE]

Chemopreventative

Biochem Pharmacol. 2004 Aug 1;68(3):453-62.

Molecular mechanisms in C-Phycocyanin induced apoptosis in human chronic myeloid leukemia cell line-K562.

Subhashini J, Mahipal SV, Reddy MC, Mallikarjuna Reddy M, Rachamallu A, Reddanna P.

Department of Animal Sciences, School of Life Sciences, University of Hyderabad, Hyderabad 500046, India.

C-Phycocyanin (C-PC), the major light harvesting biliprotein from Spirulina platensis is of greater importance because of its various biological and pharmacological properties. It is a water soluble, non-toxic fluorescent protein pigment with potent anti-oxidant, anti-inflammatory and anti-cancer properties. In the present study the effect of highly purified C-PC was tested on growth and multiplication of human chronic myeloid leukemia cell line (K562). The results indicate significant decrease (49%) in the proliferation of K562 cells treated with 50 microM C-PC up to 48 h. Further studies involving fluorescence and electron microscope revealed characteristic apoptotic features like cell shrinkage, membrane blebbing and nuclear condensation. Agarose electrophoresis of genomic DNA of cells treated with C-PC showed fragmentation pattern typical for apoptotic cells. Flow cytometric analysis of cells treated with 25 and 50 microM C-PC for 48 h showed 14.11 and 20.93% cells in sub-G0/G1 phase, respectively. C-PC treatment of K562 cells also resulted in release of cytochrome c into the cytosol and poly(ADP) ribose polymerase (PARP) cleavage. These studies also showed down regulation of anti-apoptotic Bcl-2 but without any changes in pro-apoptotic Bax and thereby tilting the Bcl-2/Bax ratio towards apoptosis. These effects of C-PC appear to be mediated through entry of C-PC into the cytosol by an unknown mechanism. The present study thus demonstrates that C-PC induces apoptosis in K562 cells by cytochrome c release from mitochondria into the cytosol, PARP cleavage and down regulation of Bcl-2.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15242812 [PubMed - indexed for MEDLINE]

Chemopreventative

Biotechnol Appl Biochem. 2007 Jul;47(Pt 3):159-67.

Alteration of mitochondrial membrane potential by Spirulina platensis C-phycocyanin induces apoptosis in the doxorubicinresistant human hepatocellular-carcinoma cell line HepG2.

Roy KR, Arunasree KM, Reddy NP, Dheeraj B, Reddy GV, Reddanna P.

Department of Animal Sciences, School of Life Sciences, University of Hyderabad, Hyderabad, India.

C-PC (C-phycocyanin) is a water-soluble biliprotein from the filamentous cyanobacterium Spirulina platensis with potent antioxidant, anti-inflammatory and anticancerous properties. In the present study, the effect of C-PC was tested on the proliferation of doxorubicin-sensitive (S-HepG2) and -resistant (R-HepG2) HCC (hepatocellular carcinoma) cell lines. These studies indicate a 50% decrease in the proliferation of S- and R-HepG2 cells treated with 40 and 50 microM C-PC for 24 h respectively. C-PC also enhanced the sensitivity of R-HepG2 cells to doxorubicin. R-HepG2 cells treated with C-PC showed typical apoptotic features such as membrane blebbing and DNA fragmentation. Flow-cytometric analysis of R-HepG2 cells treated with 10, 25 and 50 microM C-PC for 24 h showed 18.8, 39.72 and 65.64% cells in sub-G(0)/G(1)-phase respectively. Cytochrome c release, decrease in membrane potential, caspase 3 activation and PARP [poly(ADP-ribose) polymerase] cleavage were observed in C-PC-treated R-HepG2 cells. These studies also showed down-regulation of the anti-apoptotic protein Bcl-2 and up-regulation of the pro-apoptotic Bax (Bcl2-associated X-protein) protein in the R-HepG2 cells treated with C-PC. The present study thus demonstrates that C-PC induces apoptosis in R-HepG2 cells and its potential as an anti-HCC agent.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17274761 [PubMed - indexed for MEDLINE]

Chemopreventative

Phytother Res. 1999 Mar;13(2):111-4.

Modulatory potential of Spirulina fusiformis on carcinogen metabolizing enzymes in Swiss albino mice.

Mittal A, **Kumar PV**, **Banerjee S**, **Rao AR**, **Kumar A**.

Department of Zoology, University of Rajasthan, Jaipur, India.

The modulatory potential of Spirulina fusiformis was observed on the hepatic and extrahepatic carcinogen metabolizing enzymes in Swiss albino mice at a dose of 800 mg/kg b.w. given orally. A significant reduction in the hepatic cytochrome P-450 content was observed in the group treated with Spirulina in comparison with the control group. The hepatic glutathione S-transferase activity was induced significantly by Spirulina treatment. There was no change in the extrahepatic glutathione S-transferase activity after the animals were fed with Spirulina.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 10190182 [PubMed - indexed for MEDLINE]

Chemopreventative

Sheng Wu Yi Xue Gong Cheng Xue Za Zhi. 2002 Jan;19(1):1-3.

[Inhibition activity of spirulina platensis proteins photo-immobilization biomaterial on proliferation of cancer cells]

[Article in Chinese]

Guan Y, **Guo B**.

Biotechnology Research Institute, South China Normal University, Guangzhou 510631.

The bioactive protein-phycocyanin and all the proteins of Spirulina Platensis were isolated and purified. Photo-reactive proteins were synthesized by coupling the proteins with (N-(4-azidobenzoyloxy)succinimide) and were spread onto the 24-well cell culture polystyrene plate. Then the coated surface was exposed to ultraviolet irradiation for chemical fixation of proteins via the conversion of the phenylazido group to the highly reactive phenyl-nitrene which spontaneously formed covalent bonds with neighboring hydrocarbons. On these proteins-immobilized polystyrene plates, the liver cancer cells 7402 were cultured under the serum-free conditions, and the inhibition activity on proliferation of liver cancer cells was investigated and analyzed.

Publication Types:

- English Abstract
- Research Support, Non-U.S. Gov't

PMID: 11951491 [PubMed - indexed for MEDLINE]

Chemopreventative

Acta Pharmacol Sin. 2001 Dec;22(12):1121-4.

Chemo- and radio-protective effects of polysaccharide of Spirulina platensis on hemopoietic system of mice and dogs.

Zhang HQ, **Lin AP**, **Sun Y**, **Deng YM**.

The Medical and Pharmaceutical Academe of Yangzhou University, Yangzhou 225001, China.

AIM: To observe polysaccharide of Spirulina platensis (PSp) on the hematopoietic system of mouse and dogs which were damaged by injection of cyclophosphamide (CTX) and 60Co-gamma irradiation. METHODS: CTX and 60Co gamma ray were used to induce bone marrow damage, and the experimental animals were ig with different dose of PSp in vivo, after 12-d and 21-d administration, the whole blood cells and nucleated cells in bone marrow were measured, and the DNA in bone marrow were inspected by UV-spectrophotometer. RESULTS: CTX and 60Co-gamma irradiation induced hemopoietic system damage in mice and dogs, respectively. PSp 30, 60 mg/kg increased the level of the white cells in blood and nucleated cells and DNA in bone marrow in mice but had no effects on red cells and hemoglobins. PSp 12 mg/kg increased the level of red cells, white cells, and hemoglobins in blood and nucleated cells in bone marrow in dogs ($P < 0.01$), and the effects of PSp 60 mg/kg were better than that of berbamine hydrochloride 60 mg/kg. CONCLUSION: PSp has chemo-protective and radio-protective capability, and may be a potential adjunct to cancer therapy.

PMID: 11749812 [PubMed - indexed for MEDLINE]

Chemopreventative

Mol Cell Biochem. 2001 Oct;226(1-2):27-38.

Chemomodulation of carcinogen metabolising enzymes, antioxidant profiles and skin and forestomach papillomagenesis by Spirulina platensis.

Dasgupta T, **Banejee S**, **Yadav PK**, **Rao AR**.

Cancer Biology and Applied Molecular Biology Laboratories, School of Life Sciences, Jawaharlal Nehru University, New Delhi, India.

Numerous reports have revealed an inverse association between consumption of some selective natural products and risk of developing cancer. In the present study the effect of 250 and 500 mg/kg body wt. of Spirulina was examined on drug metabolising phase I and phase II enzymes, antioxidant enzymes, glutathione content, lactate dehydrogenase and lipid peroxidation in the liver of 7-week-old Swiss albino mice. The implications of these biochemical alterations have been further evaluated adopting the protocol of benzo(a)pyrene induced forestomach and 7,12 dimethylbenz(a)anthracene (DMBA) initiated and croton oil promoted skin papillomagenesis. Our primary findings reveal the 'Monofunctional' nature of Spirulina as deduced from its potential to induce only the phase II enzyme activities associated mainly with carcinogen detoxification. The glutathione S-transferase and DT-diaphorase specific activities were induced in hepatic and all the extrahepatic organs examined (lung, kidney and forestomach) by Spirulina pretreatment (significance level being from $p < 0.05$ to $p < 0.005$) except for the low dose treatment in forestomach. With reference to antioxidant enzymes viz., superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase and reduced glutathione were increased significantly by both the chosen doses of Spirulina from $p < 0.01$ to $p < 0.005$. Chemopreventive response was quantitated by the average number of papillomas per effective mouse (tumor burden) as well as percentage of tumor bearing animals. There was a significant inhibition of tumor burden as well as tumor incidence in both the tumor model systems studied. In the skin tumor studies tumor burden was reduced from 4.86 to 1.20 and 1.15 by the low and high dose treatment respectively. In stomach tumor studies tumor burden was 2.05 and 1.73 by the low and high doses of Spirulina treatment against 3.73 that of control.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 11768236 [PubMed - indexed for MEDLINE]

Chemopreventative

Toxicol Lett. 1989 Aug;48(2):165-9.

Radioprotective effect of extract from Spirulina platensis in mouse bone marrow cells studied by using the micronucleus test.

Qishen P, Guo BJ, Kolman A.

Department of Biotechnology, Zhongkai Agriculture and Technology College, Guangzhou People's Republic of China.

The radioprotective effect of an extract of Spirulina platensis has been studied using the micronucleus test in polychromatic erythrocytes of bone marrow of mice. In this system the extract caused a significant reduction of the micronucleus frequencies induced by gamma-radiation.

PMID: 2505406 [PubMed - indexed for MEDLINE]

Chemopreventative

Eur J Cancer Clin Oncol. 1988 May;24(5):839-50.

Tumor necrosis factor in experimental cancer regression with alphatocopherol, beta-carotene, canthaxanthin and algae extract.

Shklar G, Schwartz J.

Department of Oral Medicine and Oral Pathology, Harvard School of Dental Medicine, Boston, MA 02115.

Regression of established hamster buccal pouch carcinoma has recently been demonstrated in association with an induction of tumor necrosis factor alpha in macrophages. Regression of hamster buccal pouch tumors has also been demonstrated following the local injection of alphatocopherol, canthaxanthin and an extract of Spirulina-Dunaliella algae. The current study demonstrates that cancer regression is also accompanied by a significant induction of tumor necrosis factor in macrophages in the tumor area, suggesting a possible mechanism of tumor destruction. One hundred and forty young, male adult hamsters were divided into seven equal groups of 20 animals. Epidermoid carcinomas were induced in right buccal pouches by 14 weeks of painting, three times per week, of a 0.5% solution of 7,12-dimethylbenz(a)anthracene. Groups 1 and 2 were untreated and sham injected controls. Groups 3-7 had injected twice weekly into the right buccal pouches 0.1 ml (1.9 mg/ml of 13-cis-retinoic acid, canthaxanthin, algae extract, beta-carotene and alphatocopherol. After 4 weeks the tumors in groups 3-7 demonstrated varying degrees of regression and the animals were sacrificed and the right buccal pouches excised. Tumor necrosis factor alpha (TNF-alpha) was demonstrated by immunohistochemical techniques. A very significant increase in TNF-alpha positive macrophages was found in the tumor-bearing pouches of animals in groups 5-7. Smaller numbers of TNF-alpha-positive macrophages were found in group 4 pouches and a very slight increase in group 3 pouches.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 3139418 [PubMed - indexed for MEDLINE]

Chemopreventative

J Oral Maxillofac Surg. 1987 Jun;45(6):510-5.

Regression of experimental hamster cancer by beta carotene and algae extracts.

Schwartz J, Shklar G.

The effect of algae extract on tumor regression was studied. Phycotene (extract of Spirulina and Dunaliella algae) 250 micrograms in 0.1 ml MEM (minimum essential medium) was injected locally into DMBA (7, 12 dimethylbenz(a)anthracene)-induced squamous cell carcinomas of hamster buccal pouch in 20 animals. DMBA-induced carcinomas in 20 hamsters were injected locally with beta carotene 250 micrograms in 0.1 ml MEM; DMBA-induced carcinomas in 20 animals were injected locally with canthaxanthin, 250 micrograms in 0.1 ml MEM, and DMBA-induced carcinomas in 20 animals were injected locally with 13-cis-retinoic acid, 250 micrograms in 0.1 ml MEM. Twenty animals with DMBA-induced carcinomas were sham-injected controls using 0.1 ml MEM. The various agents were injected into the tumor bearing right buccal pouches twice-weekly for four weeks. Total tumor regression was found in 30% of phycotene animals, 20% of beta carotene animals and 15% of canthaxanthin animals after four weeks. Partial tumor regression was found in the remaining 70% of phycotene animals, 80% of beta carotene animals and 85% of canthaxanthin animals. None of the 13-cis-retinoic acid animals had total tumor regression, but 70% showed partial regression. No tumor regression was found in the DMBA control group and the sham-injected group.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 3108474 [PubMed - indexed for MEDLINE]

Chemopreventative

Cancer Sci. 2009 May 6. [Epub ahead of print]

Enhancement of antitumor natural killer cell activation by orally administered Spirulina extract in mice.

Akao Y, **Ebihara T**, **Masuda H**, **Saeki Y**, **Akazawa T**, **Hazeki K**, **Hazeki O**, **Matsumoto M**, **Seya T**.

Department of Microbiology and Immunology, Hokkaido University Graduate School of Medicine, Kita-15, Nishi-7, Kita-ku Sapporo 060-8638, Japan.

Oral administration of hot-water extract of Spirulina, cyanobacterium Spirulina platensis, leads to augmentation of NK cytotoxicity in humans. Here, we applied to syngeneic tumor-implant mice (C57BL/6 versus B16 melanoma) Spirulina to elucidate the mechanism of raising antitumor NK activation. A B16D8 subcell line barely expressed MHC class I but about 50% expressed Rae-1, a ligand for NK activation receptor NKG2D. The Rae-1-positive population of implant B16 melanoma was effectively eliminated in the tumor mass progressed in mice. This antitumor activity was induced in parallel with IFN-gamma and abolished in mice by treatment with asialoGM-1 but not CD8beta Ab, suggesting the effector is NK cell. NK cell activation occurred in the spleen of wild-type mice medicated with Spirulina. This Spirulina-mediated enhanced NK activation was abrogated in MyD88 -/- mice but not in TICAM-1 -/- mice. The NK activating properties of Spirulina depending on MyD88 were confirmed with in vitro bone marrow-derived dendritic cells expressing TLR2/4. In D16D8 tumor challenge studies, the antitumor effect of Spirulina was abolished in MyD88 -/- mice. Hence, orally administered Spirulina enhances tumoricidal NK activation through the MyD88 pathway. Spirulina exerted a synergistic antitumor activity with BCG-cell wall skeleton, which is known to activate the MyD88 pathway via TLR2/4 with no NK enhancing activity. Spirulina and BCG-cell wall skeleton synergistically augmented IFN-gamma production and antitumor potential in the B16D8 versus C57BL/6 system. We infer from these results that NK activation by Spirulina has some advantage in combinational use with BCG-cell wall skeleton for developing adjuvant-based antitumor immunotherapy. (Cancer Sci 2009).

PMID: 19432881 [PubMed - as supplied by publisher]

Chemopreventative

Med Oncol. 2009 Jan 21. [Epub ahead of print]

Long-term effect of Spirulina platensis extract on DMBA-induced hamster buccal pouch carcinogenesis (immunohistochemical study).

Grawish ME, Zaher AR, Gaafar AI, Nasif WA.

Oral Biology Department, Faculty of Dentistry, Mansoura University, Mansoura, Egypt, grawish2005@yahoo.com.

In cancer research, the use of complementary and alternative medicine has increased over the past decade. In this study, 80 male golden Syrian hamsters were divided into four equal groups; the right buccal pouches of the hamster rats in group 1 were painted with 0.5% solution of 7, 12-dimethylbenz[a]anthracene (DMBA), three times a week for 32 weeks. The same pouches of group 2 were subjected to the same DMBA painting; but at the same time, the animals received 10 mg/daily Spirulina platensis extract for the same period. In group 3, the same regimen of DMBA painting was done but for 24 weeks only and the daily systemically S. platensis was received for the 32 weeks. In group 4, neither DMBA painting nor S. platensis administration was done but pouches were painted with saline and served as a control one. Five rats from each group were sacrificed at 12, 24, 28, and 32 weeks, respectively. The required pouches were excised, fixed, and embedded in paraffin to be immunostained with proliferating cell nuclear antigen (PCNA). The results showed that increased PCNA expression was directly related to the severity of pathological alterations from normal epithelium to dysplasia and from dysplasia to squamous cell carcinoma (SCC) in the study groups at the different extended periods of DMBA application and S. platensis extract administration. Analysis of variance and Duncan's multiple-range test for PCNA labeling index were proved a high significant difference ($P < 0.01$) between the different groups. From the pervious results, it can be concluded that S. platensis extract has a beneficial role in regression of cancer progression.

PMID: 19156551 [PubMed - as supplied by publisher]

Chemopreventative

Food Chem Toxicol. 2008 Feb;46(2):567-74. Epub 2007 Sep 5.

Chemoprotective effect of Spirulina (Arthrospira) against cyclophosphamide-induced mutagenicity in mice.

Chamorro-Cevallos G, **Garduño-Siciliano L**, **Barrón BL**, **Madrigal-Bujaidar E**, **Cruz-Vega DE**, **Pages N**.

Departamento de Farmacia, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prolongación Carpio y Plan de Ayala S/N, 11340 México D.F., México. gchamcev@yahoo.com.mx

The aim of this study was to investigate the antimutagenic effects of Spirulina (SP) on male and female mice by the dominant lethal test using cyclophosphamide (CP) as a mutagen. Animals of both sex were given SP orally at 0, 200, 400 or 800 mg/kg body weight (b.w.) for 2 weeks prior to starting the CP treatment. CP was i.p. injected daily for 5 days at 40 mg/kg b.w. For the male-dominant lethal test, each male was caged with untreated females per week for 3 weeks. For the female-dominant lethal test the above doses and schedule treatments were used and treated females were caged for one week with untreated males (1-2). On days 13-15 after breeding was |started all the females were evaluated for incidence of pregnancy, total corpora lutea, total implants and pre- and post-implant losses. In the male-dominant lethal test, the CP induced pre- and post-implant losses in untreated females were inhibited at all SP doses. In the female-dominant lethal test only post-implantation losses were prevented at the same doses. Semen examination of a separate group of mice showed that SP improved its quality. Our results illustrate protective effects of SP in relation to CP-induced genetic damage to germ cells.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17928122 [PubMed - indexed for MEDLINE]

Chemopreventative

Vopr Pitan. 1999;68(1):17-9.

[Effect of biologically active food additives containing autolysate of baker's yeast and spirulina on intestinal permeability in an experiment]

[Article in Russian]

Mazo VK, **Gmoshinskiĭ IV**, **Sokolova AG**, **Zorin SN**, **Danilina LL**, **Litvinova AV**, **Radchenko SN**.

Influence of bioactive food supplements (BFA) intake on intestinal barrier permeability to macromolecules of polyethylene glycol 4000 was studied in rats with intestinal anaphylaxis and after external gamma-irradiation. BFA studied included autolysed baker's yeast ("Vitasil") and edible algae Spirulina platensis. Intake of complex additive Vitasil + Spirulina resulted in significant diminution of permeability before irradiation and its partial normalization (24% decrease) after irradiation. Spirulina additive intake led to practically complete normalization of permeability (1.84 times decrease) in anaphylactic rats. It is concluded that Spirulina and Vitasil are promising BFA for organism general resistance elevation.

Publication Types:

- English Abstract

PMID: 10198958 [PubMed - indexed for MEDLINE]

Yao Xue Xue Bao. 2002 Aug;37(8):616-20.

[Effect of polysaccharide from Spirulina platensis on hematopoietic cells proliferation, apoptosis and Bcl-2 expression in mice bearing tumor treated with chemotherapy]

[Article in Chinese]

Liu XM, **Zhang HQ**.

Medical and Pharmacological Institute of Yangzhou University, Yangzhou 225001, China. xiaoning-liu@263.net

AIM: To evaluate the effect of polysaccharide from Spirulina platensis (PSP) on hematopoietic cell proliferation, apoptosis and Bcl-2 expression in mice bearing tumor treated with chemotherapy. METHODS: The model of chemotherapy for transplant solid tumor in mice was established. The hematopoietic cell proliferation, apoptosis, Bcl2 expression and related cytokines were assayed by the technique of culture of hematopoietic progenitor cell, fluoromicroscope and light microscope, immunohistochemical method, and double antibody sandwich ELISA. RESULTS: PSP significantly ameliorated CFU-GM proliferation inhibition and hematopietic cells apoptosis induced by CTX. Moreover, PSP evidently increased the content of IL-1, IL-3, GM-CSF and TNF-alpha in serum and Bcl-2 expression of hematopoietic cells. CONCLUSION: PSP indirectly upregulated Bcl-2 expression of hematopoietic cells by promoting endogenous cytokines secretion which may be one of the mechanisms, by which PSP enhanced hematopoietic cell proliferation and inhibited its apoptosis in mice bearing tumor treated with chemotherapy.

Publication Types:

- English Abstract

PMID: 12567775 [PubMed - indexed for MEDLINE]

Chemopreventative

Zhonghua Yu Fang Yi Xue Za Zhi. 1995 Jan;29(1):13-7.

[Inhibitive effects of spirulina on aberrant crypts in colon induced by dimethylhydrazine]

[Article in Chinese]

Chen F, **Zhang Q**.

Hengyang Medical College, Hengyang Hunan.

Precancerous pathological changes of colon was induced by single injection in a short-term and multiple injection in a long-term intraperitoneally with 1,2-dimethylhydrazine (DMH) in NIH mice and Sprague-Dawley rats. And, protective effects of spirulina, germanium-132 and vitamin E on colon aberrant crypts induced by DMH were observed. Results showed either single injection or multiple injection with DMH could induce aberrant crypts in colon. The number of aberrant crypts scattered by short-term single injection was less than that by multiple one, and less of the aberrant crypts foci were formed by short-term single injection. Spirulina powder, germanium-132 and vitamin E all could inhibit the function of aberrant crypts of colon. In the ninth week during multiple injection with DMH, a lot of aberrant crypts of colon had been induced, and a certain amount of aberrant crypts foci had been generated. The number of aberrant crypts and aberrant crypts foci in the animals with tumor increased with the length of DMH injection. In the ninth-, 13th- and 16th-week, respectively, the number of aberrant crypts and aberrant crypts foci was significantly less in animals protected by spirulina than in positive controls ($P < 0.01$), but there was no significant difference between them during 21st- and 24th-week of injections.

Publication Types:

- English Abstract
- Research Support, Non-U.S. Gov't

PMID: 7600882 [PubMed - indexed for MEDLINE]

Chemopreventative

Curr Pharm Biotechnol. 2005 Oct;6(5):373-9.

Nutritional and therapeutic potential of Spirulina.

Khan Z, **Bhadouria P**, **Bisen PS**.

Department of Biotechnology, J.C. Bose Institute of Life Sciences, Bundelkhand University, Jhansi 284128, U.P., India.

Spirulina, a filamentous cyanobacterium, possesses diverse biological activities and nutritional significance due to high concentration of natural nutrients, having bio-modulatory and immuno-modulatory functions. Different Spirulina preparations influence immune system viz. increase phagocytic activity of macrophages, stimulating the production of antibodies and cytokines, increase accumulation of NK cells into tissue and activation and mobilization of T and B cells. Spirulina have also shown to perform regulatory role on lipid and carbohydrate metabolism by exhibiting glucose and lipid profile correcting activity in experimental animals and in diabetic patients. Preparations have been found to be active against several enveloped viruses including herpes virus, cytomegalovirus, influenza virus and HIV. They are capable to inhibit carcinogenesis due to anti-oxidant properties that protect tissues and also reduce toxicity of liver, kidney and testes.

Publication Types:

- Review

PMID: 16248810 [PubMed - indexed for MEDLINE]

Chemopreventative

Oral Oncol. 2008 Oct;44(10):956-62. Epub 2008 Feb 8.

Effects of Spirulina platensis extract on Syrian hamster cheek pouch mucosa painted with 7,12-dimethylbenz[a]anthracene.

Grawish ME.

Faculty of Dentistry, Mansoura University, Mansoura, Egypt.
grawish2005@yahoo.com

Research into cancer prevention seeks to identify the preventable causes of cancer, and to reduce cancer incidence by effective implementation of preventative strategies in target populations. In this study, 30 male golden Syrian hamsters were divided into three equal groups; the right buccal pouches of the hamster rats in group one were painted with 0.5% solution of 7,12-dimethylbenz[a]anthracene (DMBA), three times a week, until sacrificed. The same pouches of group two were also painted with DMBA, but received an additional 10mg/daily Spirulina platensis extract, which was added to the soft diet supplements during the same period. The hamster rats in group three received neither DMBA nor S. platensis extract. They were painted with saline and served as control animals. Half the hamsters from each of the three groups were sacrificed by ether inhalation after 7 weeks, and the remaining half were sacrificed after 14 weeks. The required buccal pouches were surgically excised and prepared for regular H&E and argyrophilic proteins of the nuclear organizer regions (AgNOR) silver staining. AgNORs counting and statistical analysis were carried out. We observed moderate dysplastic changes extending into the midspinous layer in group one 7 weeks after DMBA painting, which reached to half the thickness of the hyperplastic epithelium after 14 weeks. However, in group two, mild dysplastic changes were observed after 7 weeks, which were restricted to the basilar and parabasilar layers of the epithelium after 14 weeks of treatment. AgNOR staining in group one produced AgNOR counts ranging from one to seven dots per nucleus, whereas the counts were one or two dots per nucleus in group two. The AgNOR mean number in groups one, two and three was (3.1+/-0.006, 1.3+/-0.003 and 1.2+/-0.003, respectively). Moreover, with one sample t-test, a significant difference was found in AgNOR mean number between groups one and two, groups one and three and between groups two and three ($P<0.05$). An overall significant difference among the three groups ($P<0.01$) was indicated with one-way analysis of variance. The pAgNOR was 10% in group one, 5% in group two and 4% in group three. Consequently, S. platensis is an adjunctive means to inhibit the dysplastic changes occurring in the hamster cheek pouch (HCP) mucosa. However, more research is needed to expand its beneficial action.

PMID: 18262461 [PubMed - indexed for MEDLINE]

Chemopreventative

Diabetes

J Med Food. 2001 Winter;4(4):193-199.

Role of Spirulina in the Control of Glycemia and Lipidemia in Type 2 Diabetes Mellitus.

Parikh P, **Mani U**, **Iyer U**.

Department of Foods and Nutrition, M S University of Baroda, Vadodara-390002, Gujarat, India.

Spirulina, with its high concentration of functional nutrients, is emerging as an important therapeutic food. This study aimed to evaluate the hypoglycemic and hypolipidemic role of Spirulina. Twenty-five subjects with type 2 diabetes mellitus were randomly assigned to receive Spirulina (study group) or to form the control group. At baseline, the control and study groups were matched for various variables. The efficacy of Spirulina supplementation (2 g/day for 2 months) was determined using the preintervention and postintervention blood glucose levels, glycosylated hemoglobin (HbA(1c)) levels, and lipid profiles of the diabetic subjects. Two-month supplementation with Spirulina resulted in an appreciable lowering of fasting blood glucose and postprandial blood glucose levels. A significant reduction in the HbA(1c) level was also observed, indicating improved long-term glucose regulation. With regard to lipids, triglyceride levels were significantly lowered. Total cholesterol (TC) and its fraction, low-density lipoprotein cholesterol (LDL-C), exhibited a fall coupled with a marginal increase in the level of high-density lipoprotein cholesterol (HDL-C). As a result, a significant reduction in the atherogenic indices, TC:HDL-C and LDL-C: HDL-C, was observed. The level of apolipoprotein B registered a significant fall together with a significant increment in the level of apolipoprotein A1. Therefore, a significant and favorable increase in the ratio of A1:B was also noted. These findings suggest the beneficial effect of Spirulina supplementation in controlling blood glucose levels and in improving the lipid profile of subjects with type 2 diabetes mellitus.

PMID: 12639401 [PubMed - as supplied by publisher]

Life Sci. 2001 Jul 20;69(9):1029-37.

Spirulina maxima prevents fatty liver formation in CD-1 male and female mice with experimental diabetes.

Rodríguez-Hernández A, Blé-Castillo JL, Juárez-Oropeza MA, Díaz-Zagoya JC.

Laboratorio de Análisis Clínicos, Hospital General de Zona No. 1, Instituto Mexicano de Seguro Social, UNAM, Ciudad Universitaria, DF.

The dietary administration of 5% Spirulina maxima (SM) during four weeks to diabetic mice, starting one week after a single dose of alloxan, 250 mg/Kg body weight, prevented fatty liver production in male and female animals. The main action of SM was on triacylglycerol levels in serum and liver. There was also a moderate hypoglycemia in male mice. The thiobarbituric acid reactive substances also decreased in serum and liver after SM administration. There was also a decrease in the percentage of HDL in diabetic mice that was reverted by the SM administration. The sum of LDL + VLDL percentages was also partially normalized in diabetic animals by the SM administration. An additional observation was the lower incidence of adherences between the liver and the intestine loops in the diabetic mice treated with SM compared with diabetic mice without SM. Male and female mice showed differences to diabetes susceptibility and response to SM, the female being more resistant to diabetes induction by alloxan and more responsive to the beneficial effects of SM. It is worth future work of SM on humans looking for better quality of life and longer survival of diabetic patients.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 11508645 [PubMed - indexed for MEDLINE]

Vopr Pitan. 2004;73(5):17-20.

[Effect of food diet supplements with chromium on the clinical and metabolic parameters in type 2 diabetic patients]

[Article in Russian]

Sharafetdinov KhKh, **Meshcheriakova VA**, **Plotnikova OA**, **Mazo VK**, **Gmoshinskiĭ IV**, **Nechaeva SV**.

It was investigated the influence of food diet supplements with chromium on dynamic of glycaemia, lipid profile, blood pressure and weight in type 2 diabetic patients. Traditional hypocaloric diet was supplemented with chromium-spirulina (50 mcg chromium per day). The results investigations indicated that a chromium-enriched diet has beneficial effects on basal and postprandial glycaemia, the content of cholesterol and triglycerides in serum in compared with a traditional hypocaloric diet.

Publication Types:

- English Abstract

PMID: 15754482 [PubMed - indexed for MEDLINE]

Vopr Pitan. 2004;73(4):17-20.

[Effect of a zinc-enriched diet on the clinical and metabolic parameters in type 2 diabetic patients]

[Article in Russian]

Sharafetdinov KhKh, **Meshcheriakov VA**, **Plotnikova OA**, **Mazo VK**, **Gmoshinskiĭ IV**, **Aleshko-Ozhevskiĭ IuP**, **Sheviakova LV**, **Makhova NN**.

It was investigated the influence of a diet with zinc supplementation on dynamic of glycaemia, lipid profile, blood pressure and weight in type 2 diabetic patients. Traditional hypocaloric diet was supplemented with zinc-spirulina (7.5 mg zinc per day). The results investigations indicated that a zinc-enriched diet has beneficial effects on basal and postprandial glycaemia, the content of cholesterol and triglycerides in serum in compared with a traditional hypocaloric diet.

Publication Types:

- Comparative Study
- English Abstract

PMID: 15460984 [PubMed - indexed for MEDLINE]

Zhongguo Zhong Yao Za Zhi. 2005 Feb;30(3):211-5.

[Protective effects of polysacchride of Spirulina platensis and Sargassum thunbeergii on vascular of alloxan induced diabetic rats]

[Article in Chinese]

Huang ZX, **Mei XT**, **Xu DH**, **Xu SB**, **Lv JY**.

School of Pharmaceutical Sciences, SunYat-sen University, Guangzhou 510275, China.

OBJECTIVE: To study the protective effects of polysaccharide of Spirulina platensis and Sargassum thunbeergii on vascular of alloxan (ALX) induced diabetic rats. METHOD: With the doses of polysaccharide of Spirulina platensis (PSP) and Sargassum thunbeergii (PST) compound (1:1) 12.261, 36.783, 110.349 mg x kg(-1) by i.g. administration to alloxan induced diabetic rats respectively for 6 weeks. Then the blood glucose and the TC, HDL-C, TG, NO, ET in serum were detected. The contraction and relaxation response to NE and ACh in aortic rings of the alloxan induced diabetic rats has been studied. RESULT: The results showed the compound of PSP and PST could decrease the blood glucose and the TC, TG, NO, ET in serum and increase HDL-C than in the alloxan induced diabetic rats. The contraction responses to NE in aortic rings of the alloxan induced diabetic rats were significantly elevated in the normal rats, and the responses to ACh were significantly lower. PSP and PST compound could significantly lower the responses to NE and significantly elevate the responses to ACh in aortic rings of the alloxan induced diabetic rats. CONCLUSION: PSP and PST compound could decrease blood glucose and could protect the vascular of alloxan induced diabetic rats.

Publication Types:

- English Abstract

PMID: 15719643 [PubMed - indexed for MEDLINE]

Anti-Viral

Chem Pharm Bull (Tokyo). 2001 Jan;49(1):108-10

Effects of structural modification of calcium spirulan, a sulfated polysaccharide from Spirulina platensis, on antiviral activity.

Lee JB, **Srisomporn P**, **Hayashi K**, **Tanaka T**, **Sankawa U**, **Hayashi T**.

Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Japan.

Calcium ion binding with the anionic part of a molecule was replaced with various metal cations and their inhibitory effects on the replication of herpes simplex virus type 1 were evaluated. Replacement of calcium ion with sodium and potassium ions maintained the antiviral activity while divalent and trivalent metal cations reduced the activity. Depolymerization of sodium spirulan with hydrogen peroxide decreased in antiviral activity as its molecular weight decreased.

PMID: 11201213 [PubMed - indexed for MEDLINE]

J Acquir Immune Defic Syndr Hum Retrovirol. 1998 May 1;18(1):7-12.

Inhibition of HIV-1 replication by an aqueous extract of Spirulina platensis (Arthrospira platensis).

Ayehunie S, **Belay A**, **Baba TW**, **Ruprecht RM**.

Laboratory of Viral Pathogenesis, Dana-Farber Cancer Institute, and Harvard Medical School, Boston, Massachusetts 02115, USA.

An aqueous extract of the blue-green filamentous algae Arthrospira platensis (previously called Spirulina platensis) inhibited HIV-1 replication in human T-cell lines, peripheral blood mononuclear cells (PBMC), and Langerhans cells (LC). Extract concentrations ranging between 0.3 and 1.2 microg/ml reduced viral production by approximately 50% (50% effective concentration [EC50]) in PBMCs. The 50% inhibitory concentration (IC50) of extract for PBMC growth ranged between 0.8 and 3.1 mg/ml. Depending on the cell type used, therapeutic indices ranged between 200 and 6000. The extract inactivated HIV-1 infectivity directly when preincubated with virus before addition to human T-cell lines. Fractionation of the extract revealed antiviral activity in the polysaccharide fraction and also in a fraction depleted of polysaccharides and tannins. We conclude that aqueous A platensis extracts contain antiretroviral activity that may be of potential clinical interest.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9593452 [PubMed - indexed for MEDLINE]

Anti-Viral

AIDS Res Hum Retroviruses. 1996 Oct 10;12(15):1463-71.

A natural sulfated polysaccharide, calcium spirulan, isolated from Spirulina platensis: in vitro and ex vivo evaluation of anti-herpes simplex virus and anti-human immunodeficiency virus activities.

Hayashi K, **Hayashi T**, **Kojima I**.

Department of Virology, Toyama Medical and Pharmaceutical University, Japan.

A sulfated polysaccharide named calcium spirulan (Ca-SP) has been isolated from a sea alga, Spirulina platensis, as an antiviral component. The anti-human immunodeficiency virus type 1 (HIV-1) and anti-herpes simplex virus type 1 (HSV-1) activities of Ca-SP were compared with those of dextran sulfate (DS) as a representative sulfated polysaccharide. Anti-HIV-1 activities of these agents were measured by three different assays: viability of acutely infected CD4-positive cells, or a cytopathology assay; determination of HIV-1 p24 antigen released into culture supernatants; and inhibition of HIV-induced syncytium formation. Anti-HSV-1 activity was assessed by plaque yield reduction. In addition, their effects on the blood coagulation processes and stability in the blood were evaluated. These data indicate that Ca-SP is a potent antiviral agent against both HIV-1 and HSV-1. Furthermore, Ca-SP is quite promising as an anti-HIV agent because even at low concentrations of Ca-SP an enhancement of virus-induced syncytium formation was not observed, as was observed in DS-treated cultures, Ca-SP had very low anticoagulant activity, and showed a much longer half-life in the blood of mice when compared with that of DS. Thus, Ca-SP can be a candidate agent for an anti-HIV therapeutic drug that might overcome the disadvantages observed in many sulfated polysaccharides. When the role of chelation of calcium ion with sulfate groups was examined by removing calcium or its replacement by sodium, the presence of calcium ion in the molecule was shown to be essential for the dose-dependent inhibition of cytopathic effect and syncytium formation induced by HIV-1.

PMID: 8893054 [PubMed - indexed for MEDLINE]

Anti-Viral

J Nat Prod. 1996 Jan;59(1):83-7.

Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga Spirulina platensis.

Hayashi T, **Hayashi K**, **Maeda M**, **Kojima I**.

Faculty of Pharmaceutical Sciences and School of Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan.

Bioactivity-directed fractionation of a hot H2O extract from a blue-green alga Spirulina platensis led to the isolation of a novel sulfated polysaccharide named calcium spirulan (Ca-SP) as an antiviral principle. This polysaccharide was composed of rhamnose, ribose, mannose, fructose, galactose, xylose, glucose, glucuronic acid, galacturonic acid, sulfate, and calcium. Ca-SP was found to inhibit the replication of several enveloped viruses, including Herpes simplex virus type 1, human cytomegalovirus, measles virus, mumps virus, influenza A virus, and HIV-1. It was revealed that Ca-SP selectively inhibited the penetration of virus into host cells. Retention of molecular conformation by chelation of calcium ion with sulfate groups was suggested to be indispensable to its antiviral effect.

PMID: 8984158 [PubMed - indexed for MEDLINE]

Med Hypotheses. 2004;62(4):507-10.

Algae -- a poor man's HAART?

Teas J, **Hebert JR**, **Fitton JH**, **Zimba PV**.

Health Promotion Education and Behavior, The Norman J Arnold School of Public Health, University of South Carolina and the South Carolina Cancer Center, 15 Medical Park, Suite 301 Columbia, SC 29203, USA. jane.teas@palmettohealth.org

Drawing inferences from epidemiologic studies of HIV/AIDS and in vivo and in vitro HIV inhibition by algae, we propose algal consumption as one unifying characteristic of countries with anomalously low rates. HIV/AIDS incidence and prevalence in Eastern Asia (approximately 1/10000 adults in Japan and Korea), compared to Africa (approximately 1/10 adults), strongly suggest that differences in IV drug use and sexual behavior are insufficient to explain the 1000-fold variation. Even in Africa, AIDS/HIV rates vary. Chad has consistently reported low rates of HIV/AIDS (2-4/100). Possibly not coincidentally, most people in Japan and Korea eat seaweed daily and the Kanemba, one of the major tribal groups in Chad, eat a blue green alga (Spirulina) daily. Average daily algae consumption in Asia and Africa ranges between 1 and 2 tablespoons (3-13 g). Regular consumption of dietary algae might help prevent HIV infection and suppress viral load among those infected.

Publication Types:

- Comparative Study

PMID: 15050097 [PubMed - indexed for MEDLINE]

Antiviral Res. 2002 Dec;56(3):279-85.

Antiviral activity of Spirulina maxima against herpes simplex virus type 2.

Hernández-Corona A, **Nieves I**, **Meckes M**, **Chamorro G**, **Barron BL**.

Departamento de Microbiologi;a, Escuela Nacional de Ciencias Biológicas, IPN, Carpio y Plan de Ayala S/N Casco de Santo Tomás, Apartado Postal 102, México, DF 11340, Mexico.

Spirulina has been used in a variety of practical applications in biotechnology and medical sciences. This paper presents the antiviral activity found in a hot water extract (HWE) of a commercial preparation of Spirulina maxima, studied by a microplate inhibition assay, using several viruses. The HWE inhibited the infection for: herpes simplex virus type 2 (HSV-2), pseudorabies virus (PRV), human cytomegalovirus (HCMV), and HSV-1, and the 50% effective inhibition doses (ED(50)) were 0.069, 0.103, 0.142, and 0.333 mg/ml for each virus, respectively. For adenovirus the inhibition was less than 20%, and no inhibition was found for measles virus, subacute sclerosing panencephalitis virus (SSPE), vesicular stomatitis virus (VSV), poliovirus 1 and rotavirus SA-11, at concentrations of 2 mg/ml of the HWE. The highest antiviral activity was for HSV-2, with a selectivity index of 128. The antiviral activity was not due to a virucidal effect. Herpesvirus infection was inhibited at the initial events (adsorption and penetration) of the viral cycle. To initiate the isolation and identification of the compound that exhibits the antiviral activity of S. maxima, some extracts made by using several solvents with different polarity were evaluated by microplate inhibition assay using HSV-2. The highest antiviral activity was detected in the methanol-water 3:1, which suggests that the antiviral activity is probably due to highly polar compounds.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 12406511 [PubMed - indexed for MEDLINE]

Zh Mikrobiol Epidemiol Immunobiol. 2002 Nov-Dec;(6):18-21.

[Action of Spirulina platensis on bacterial viruses]

[Article in Russian]

Gorobets OB, **Blinkova LP**, **Baturo AP**.

Mechnikov Research Institute for Vaccines and Sera, Moscow, Russia.

The impact of the biomass of the blue-green microalga (cyanobacterium) S. platensis on bacteriophage T4 (bacterial virus) has been evaluated. The study revealed that the addition of S. platensis biomass into the agar nutrient medium, followed by sterilization with 2% chloroform and thermal treatment, produced an inhibiting or stimulating effect on the reproduction of the bacteriophage in Escherichia coli B cells, depending on the concentration of S. platensis and the multiplicity of phage infection, as well as on the fact whether the microalgae were added during the first cycle of the development of the virus. The reproduction of the bacteriophage in E. coli B was influenced by the method and duration of the sterilization of the nutrient medium with S. platensis.

Publication Types:

- Comparative Study
- English Abstract

PMID: 12506621 [PubMed - indexed for MEDLINE]

Anti-Viral

Yakugaku Zasshi. 2008 Jan;128(1):61-79.

[Studies on evaluation of natural products for antiviral effects and their applications]

[Article in Japanese]

Hayashi T.

Graduate School of Medicine and Pharmaceutical Sciences for Research, University of Toyama, Sugitani, Toyama City, Japan. hayashi9@pha.u-toyama.ac.jp

In the search for novel antiviral molecules from natural products, we have discovered various antiviral molecules with characteristic mechanisms of action. Scopadulciol (SDC), isolated from the tropical medicinal plant Scoparia dulcis L., showed stimulatory effects on the antiviral potency of acyclovir (ACV) or ganciclovir (GCV). This effect of SDC was exerted via the activation of viral thymidine kinase (HSV-1 TK) and, as a result, an increase in the cellular concentration of the active form of ACV/GCV, i.e., the triphosphate of ACV or GCV. On the basis of these experimental results, cancer gene therapy using the HSV-1 tk gene and ACV/GCV together with SDC was found to be effective in suppressing the growth of cancer cells in animals. Acidic polysaccharides such as calcium spirulan (Ca-SP) from Spirulina platensis, nostoflan from Nostoc flagelliforme, and a fucoidan from the sporophyll of Undaria pinnatifida (mekabu fucoidan) were also found to be potent inhibitors against several enveloped viruses. Their antiviral potency was dependent on molecular weight and content of the sulfate or carboxyl group as well as counterion species chelating with sulfate groups, indicating the importance of the three-dimensional structure of the molecules. In addition, unlike dextran sulfate, Ca-SP was shown to target not only viral absorption/penetration stages but also some replication stages of progeny viruses after penetration into cells. When mekabu fucoidan or nostoflan was administered with oseltamivir phosphate, their synergistic antiviral effects on influenza A virus were confirmed in vitro as well as in vivo.

Publication Types:

- English Abstract
- Review

PMID: 18176057 [PubMed - indexed for MEDLINE]

Anti-Viral

Anemia and Blood Improvement

Ann Nutr Metab. 2005 Nov-Dec;49(6):373-80. Epub 2005 Oct 11.

Nutrition rehabilitation of HIV-infected and HIV-negative undernourished children utilizing spirulina.

Simpore J, Zongo F, Kabore F, Dansou D, Bere A, Nikiema JB, Pignatelli S, Biondi DM, Ruberto G, Musumeci S.

Unit of Formation and of Research in Sciences of Life and of the Earth, University of Ouagadougou, Burkina Faso.

The objective of this study was to assess the impact of an alimentary integrator composed of spirulina (Spirulina platensis; SP), produced at the Centre Médical St Camille of Ouagadougou, Burkina Faso, on the nutritional status of undernourished HIV-infected and HIV-negative children. We compared two groups of children: 84 were HIV-infected and 86 were HIV-negative. The duration of the study was 8 weeks. Anthropometric and haematological parameters allowed us to appreciate both the nutritional and biological effect of SP supplement to traditional meals. Rehabilitation with SP shows on average a weight gain of 15 and 25 g/day in HIV-infected and HIV-negative children, respectively. The level of anaemia decreased during the study in all children, but recuperation was less efficient among HIV-infected children. In fact 81.8% of HIV-negative undernourished children recuperated as opposed to 63.6% of HIV-infected children (Z: 1.70 (95% CI -0.366, -0.002, p = 0.088)). Our results confirm that SP is a good food supplement for undernourished children. In particular, rehabilitation with SP also seems to correct anaemia and weight loss in HIV-infected children, and even more quickly in HIV-negative undernourished children.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16219988 [PubMed - indexed for MEDLINE]

J Agric Food Chem. 2001 Mar;49(3):1625-9.

Iron availability from iron-fortified spirulina by an in vitro digestion/Caco-2 cell culture model.

Puyfoulhoux G, **Rouanet JM**, **Besançon P**, **Baroux B**, **Baccou JC**, **Caporiccio B**.

Unité Nutrition and Unité de Physiologie et Technologie Végétales, Laboratoire Génie Biologique et Sciences des Aliments, Université Montpellier II, Montpellier, France.

Iron deficiency, one of the most important nutritional problems in the world, can be caused not only by foods deficient in iron but also by poor availability of dietary iron. Iron food fortification in combination with highly available iron from supplements could effectively reduce this deficiency. The aim of this study was to examine the iron availability from iron-fortified spirulina. We have used an in vitro digestion/Caco-2 cell culture system to measure iron spirulina availability and made a comparison with those of beef, yeast, wheat floor, and iron sulfate plus ascorbic acid as a reference. Iron availability was assessed by ferritin formation in Caco-2 cells exposed to digests containing the same amount of iron. Our results demonstrate a 27% higher ferritin formation from beef and spirulina digests than from digests of yeast and wheat flour. When iron availability was expressed per microgram of iron used in each digest, a 6.5-fold increase appeared using spirulina digest in comparison with meat. In view of this observed high iron availability from spirulina, we conclude that spirulina could represent an adequate source of iron.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 11312906 [PubMed - indexed for MEDLINE]

J Agric Food Chem. 2005 Oct 5;53(20):7734-40.

C-phycocyanin, a very potent and novel platelet aggregation inhibitor from Spirulina platensis.

Hsiao G, Chou PH, Shen MY, Chou DS, Lin CH, Sheu JR.

Graduate Institute of Pharmacology, and Graduate Institute of Medical Sciences, Taipei Medical University, Taipei 110, Taiwan.

The aim of this study was to systematically examine the inhibitory mechanisms of C-phycocyanin (C-PC), one of the major phycobiliproteins of Spirulina platensis (a blue-green alga), in platelet activation. In this study, C-PC concentration-dependently (0.5-10 nM) inhibited platelet aggregation stimulated by agonists. C-PC (4 and 8 nM) inhibited intracellular Ca2+ mobilization and thromboxane A2 formation but not phosphoinositide breakdown stimulated by collagen (1 microg/mL) in human platelets. In addition, C-PC (4 and 8 nM) markedly increased levels of cyclic GMP and cyclic GMP-induced vasodilator-stimulated phosphoprotein (VASP) Ser(157) phosphorylation. Rapid phosphorylation of a platelet protein of Mw 47,000 (P47), a marker of protein kinase C activation, was triggered by phorbol-12,13-dibutyrate (150 nM). This phosphorylation was markedly inhibited by C-PC (4 and 8 nM). In addition, C-PC (4 and 8 nM) markedly reduced the electron spin resonance (ESR) signal intensity of hydroxyl radicals in collagen (1 microg/mL)-activated platelets. The present study reports on a novel and very potent (in nanomolar concentrations) antiplatelet agent, C-PC, which is involved in the following inhibitory pathways: (1) C-phycocyanin increases cyclic GMP/VASP Ser157 phosphorylation and subsequently inhibits protein kinase C activity, resulting in inhibition of both P47 phosphorylation and intracellular Ca2+ mobilization, and (2) C-PC may inhibit free radicals (such as hydroxyl radicals) released from activated platelets, which ultimately inhibits platelet aggregation. These results strongly indicate that C-PC appears to represent a novel and potential antiplatelet agent for treatment of arterial thromboembolism.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16190625 [PubMed - indexed for MEDLINE]

Br J Nutr. 2006 Feb;95(2):435-40.

Mechanisms involved in the antiplatelet effect of C-phycocyanin.

Chiu HF, **Yang SP**, **Kuo YL**, **Lai YS**, **Chou TC**.

Department of Pharmacology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan, Republic of China.

C-phycocyanin (cpc), a biliprotein isolated from Spirulina platensis, has been reported to exert many therapeutic and nutritional values. In the present study, we examined whether cpc has an antiplatelet activity in vitro and further investigated the possible anti-aggregatory mechanisms involved. Our results showed that preincubation of cpc (1-50 microg/ml) with rabbit washed platelets dose-dependently inhibited the platelet aggregation induced by collagen (10 microg/ml) or arachidonic acid (100 microm), with an IC50 of about 10 microg/ml. Furthermore, the thromboxane B2 formation caused by collagen or arachidonic acid was significantly inhibited by cpc due to suppression of cyclooxygenase and thromboxane synthase activity. Similarly, the rise of platelet intracellular calcium level stimulated by arachidonic acid and collagen-induced platelet membrane surface glycoprotein IIb/IIIa expression were also attenuated by cpc. In addition, cpc itself significantly increased the platelet membrane fluidity and the cyclic AMP level through inhibiting cyclic AMP phosphodiesterase activity. These findings strongly demonstrate that cpc is an inhibitor of platelet aggregation, which may be associated with mechanisms including inhibition of thromboxane A2 formation, intracellular calcium mobilization and platelet surface glycoprotein IIb/IIIa expression accompanied by increasing cyclic AMP formation and platelet membrane fluidity.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16469164 [PubMed - indexed for MEDLINE]

Plant Foods Hum Nutr. 1998;52(4):315-24.

Supplementary effect of spirulina on hematological status of rats during pregnancy and lactation.

Kapoor R, **Mehta U**.

Department of Home Science, Sri Sathya Sai Institute of Higher Learning Anantapur, Andhra Pradesh, India.

The effect of Spirulina on iron status was assessed based on hemoglobin, packed cell volume, serum iron, total iron binding capacity and ferritin levels of rats during pregnancy and lactation. Rats were fed 5 different kinds of diets (casein, Spirulina, wheat gluten, Spirulina + wheat gluten, Spirulina without additional vitamins and minerals) each providing 22 percent protein. Diets containing Spirulina alone or in combination with wheat gluten resulted in significantly higher iron storage and hemoglobin contents than casein and wheat gluten diets during the first half of pregnancy and lactation. Wheat gluten diet result in the smallest increase in hemoglobin levels and iron stores compared to other diets. The values of serum iron and iron binding capacity remained unchanged with different diets. Spirulina appears to be effective in improving the iron status of rats during pregnancy and lactation.

PMID: 10426118 [PubMed - indexed for MEDLINE]

Blood Coagul Fibrinolysis. 1996 Jul;7(5):554-60.

Heparin cofactor II-dependent antithrombin activity of calcium spirulan.

Hayakawa Y, Hayashi T, Hayashi K, Hayashi T, Ozawa T, Niiya K, Sakuragawa N.

Department of Clinical Laboratory Medicine, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Japan. hayakawa@ms.toyama-mpu.ac.jp

Calcium spirulan (Ca-SP), a novel sulfated polysaccharide isolated from the blue-green alga Spirulina platensis, enhanced the antithrombin activity of heparin cofactor II (HC II) more than 10000-fold. The apparent second-order rate constant of thrombin inhibition by HC II was calculated to be 4.2 x 10(4) M-1 min-1 in the absence of Ca-SP, and it increased in the presence of 50 micrograms/ml Ca-SP to 4.5 x 10(8) M-1 min-1. Ca-SP effectively induced the formation of a thrombin-HC II complex in plasma. In the presence of Ca-SP, both the recombinant HC II variants Lys173-->Leu and Arg 189-->His, which are defective in interactions with heparin and dermatan sulfate, respectively, inhibited thrombin in a manner similar to native rHC II. This result indicates that the binding site of HC II for Ca-SP is different from the heparin- or dermatan sulfate-binding site. When we removed the calcium from the Ca-SP, the compound did not exert any antithrombin activity. Furthermore, Na-SP, which was prepared by replacement of the calcium in Ca-SP with sodium, accelerated the antithrombin activity of HC II as Ca-SP did. We therefore suggest that the molecular conformation maintained by Ca or Na is indispensable to the antithrombin activity of Ca-SP. The HC II-dependent antithrombin activity of Ca-SP was almost totally abolished by treatment with chondroitinase AC I, heparinase or heparitinase, but not by treatment with chondroitinase ABC and chondroitinase AC II, suggesting that a heparin- or dermatan sulfate-like structure is not responsible for the activation of HC II by Ca-SP. Ca-SP is therefore thought to be a unique sulfated polysaccharide which shows a strong antithrombin effect in an exclusively HC II-dependent manner.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 8874866 [PubMed - indexed for MEDLINE]

Cardioprotective

J Med Food. 2002 Summer;5(2):91-6.

Hypocholesterolemic effect of spirulina in patients with hyperlipidemic nephrotic syndrome.

Samuels R, Mani UV, Iyer UM, Nayak US.

Department of Foods and Nutrition, M S University of Baroda, Vadodara, Gujarat, India.

In nephrotic syndrome, large amounts of plasma proteins are lost in urine, causing a decrease in the plasma oncotic pressure. This leads to enhanced hepatic synthesis of albumin and other proteins, including lipoproteins, causing a secondary hyperlipidemia. Essential fatty acids such as gamma-linolenic acid (GLA) can prevent accumulation of cholesterol in the body, and spirulina has an appreciable amount of GLA. In this study 23 patients (age 2 to 13 years) with nephrotic syndrome received either medication (group I) or medication plus 1 g/day Spirulina (group II). Height, weight, and serum levels of fasting blood sugar, triglycerides, total cholesterol (TC), and low- and high-density cholesterol fractions (LDL-C and HDL-C, respectively) were measured before and after the 2-month study period. Mean height and weight were normal compared with healthy, age-matched Indian children. Lipoprotein cholesterol levels were significantly increased at baseline. TC significantly decreased by 116.33 mg/dl, LDL-C by 94.14 mg/dl, and triglycerides by 67.72 mg/dl in group II; in control group I, these values fell by 69.87, 61.13, and 22.62 mg/dl, respectively. The LDL-C:HDL-C ratio also decreased significantly, by 1.66 in group II and 1.13 in group I. TC:HDL-C decreased by 1.96 in group II and 1.19 in group I. HDL-C:LDL-C also improved significantly in both the groups. It can be concluded that spray-dried Spirulina capsules, rich in antioxidants, GLA, amino acids, and fatty acids, helped reduce the increased levels of lipids in patients with hyperlipidemic nephrotic syndrome.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 12487756 [PubMed - indexed for MEDLINE]

Ann Nutr Metab. 2008;52(4):322-8. Epub 2008 Aug 19.

A randomized double-blind, placebo-controlled study to establish the effects of spirulina in elderly Koreans.

Park HJ, **Lee YJ**, **Ryu HK**, **Kim MH**, **Chung HW**, **Kim WY**.

Foods R&D, CJ CheilJedang Corp., Seoul, Korea.

AIMS: This study was conducted to determine the antioxidant capacity, immunomodulatory and lipid-lowering effects of spirulina in healthy elderly subjects and to document the effectiveness of spirulina as a functional food for the elderly. METHODS: A randomized double-blind, placebo-controlled study was performed. The subjects were 78 individuals aged 60-87 years and were randomly assigned in a blinded fashion to receive either spirulina or placebo. The elderly were instructed to consume the spirulina or placebo at home, 8 g/day, for 16 consecutive weeks. RESULTS: In male subjects, a significant plasma cholesterol-lowering effect was observed after the spirulina intervention ($p < 0.05$). Spirulina supplementation resulted in a significant rise in plasma interleukin (IL)-2 concentration, and a significant reduction in IL-6 concentration. A significant time-by-treatment intervention for total antioxidant status was observed between spirulina and placebo groups ($p < 0.05$). In female subjects, significant increases in IL-2 level and superoxide dismutase activity were observed ($p < 0.05$) after spirulina supplementation. There were significant reductions in total cholesterol in female subjects. CONCLUSIONS: The results demonstrate that spirulina has favorable effects on lipid profiles, immune variables, and antioxidant capacity in healthy, elderly male and female subjects and is suitable as a functional food. 2008 S. Karger AG, Basel.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 18714150 [PubMed - indexed for MEDLINE]

Cardioprotective

Yakugaku Zasshi. 2008 May;128(5):717-23.

[Biological activities of exogenous polysaccharides via controlling endogenous proteoglycan metabolism in vascular endothelial cells]

[Article in Japanese]

Sato T, **Yamamoto C**, **Fujiwara Y**, **Kaji T**.

Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa City, Japan.

Proteoglycan contains glycosmainoglycans, which are endogenous sulfated polysaccharides, in the molecule. The metabolism of proteoglycans regulates cell behavior and cellular events. It is possible that exogenous polysaccharide-related molecules exhibit their biological activities by two mechanisms. One is the interaction with cells and the other is the interaction with growth factors/cytokines that regulate proteoglycans. In this review, we describe sodium spirulan, a sulfated polysaccharide obtained from a hot-water extract of the blue-green alga Spirulina platensis, as an exogenous polysaccharide that stimulates the release of proteoglycans from vascular endothelial cells. Factors that regulate endothelial proteoglycan metabolism are also being described as possible target molecules of exogenous polysaccharides. Further research is required to obtain exogenous polysaccharide-related molecules that exhibit useful biological activities through controlling endothelial proteoglycan metabolism for protection against vascular lesions such as atheroslcerosis.

Publication Types:

- English Abstract
- Review

PMID: 18451618 [PubMed - indexed for MEDLINE]

Cardioprotective

Lipids Health Dis. 2007 Nov 26;6:33.

Antihyperlipemic and antihypertensive effects of Spirulina maxima in an open sample of Mexican population: a preliminary report.

Torres-Duran PV, Ferreira-Hermosillo A, Juarez-Oropeza MA.
Department of Biochemistry, School of Medicine, National Autonomous University of Mexico, P,O, Box 70-159, Mexico, D.F. 04510, Mexico. pavito@correo.unam.mx

BACKGROUND: Spirulina maxima is a filamentous cyanobacterium used as food supplement because of its high nutrient contents. It has been experimentally proven, in vivo and in vitro that posses several pharmacological properties. The purpose of this study was to evaluate the effects of Spirulina maxima orally supplied (4.5 g/day, for 6 weeks) to a sample of 36 subjects (16 men and 20 women, with ages between 18-65 years) on serum lipids, glucose, aminotransferases and on blood pressure. The volunteers did not modify their dietary habits or lifestyle during the whole experimental period. From each subject, a sample of blood was drawn in fasting state of 12 hours to determi the plasma concentrations of glucose, triacylglycerols (TAG), total cholesterol (TC), cholesterol associated to high density lipoprotein (HDL-C) and aspartate aminotransferase (AST). Anthropometric measurements including systolic (SYST-P) and diastolic (DIAST-P) blood pressure, height, weight and Body Mass Index (BMI) were also recorded. RESULTS: Comparing initial and final data, the results showed that there were no significant changes in the values of glucose and AST, but significant differences in TAG, TC, and HDL-C, were observed: TAG 233.7 +/- 177.8 vs. 167.7 +/- 100.7 mg/dL ($p < 0.001$), TC 181.7 +/- 37.5 vs. 163.5 +/- 34.4 mg/dL ($p < 0.001$), C-HDL 43.5 +/- 14.4 vs. 50 +/- 18.8 mg/dL ($p < 0.01$). The univariated analysis showed that the changes in the HDL-C and TC concentrations were dependent on TAG concentration ($p = 0.247$ and $p = 0.108$, respectively); nevertheless the calculated values for cholesterol associated to low density lipoprotein (LDL-C) were significantly reduced by the Spirulina maxima treatment but independently of the TAG changes. In addition, significant differences were found comparing initial and final SYST-P and DIAST-P blood pressure in both male and female: SYST-P male 121 +/- 9 vs. 111 +/- 8 mm Hg ($p < 0.01$), DIAST-P male 85 +/- 6.5 vs. 77 +/- 9 mm Hg ($p < 0.01$); SYST-P female 120 +/- 9.5 vs. 109 +/- 11 mm Hg ($p < 0.002$), DIAST-P female 85 +/- 11 vs. 79 +/- 7.5 mm Hg ($p < 0.03$). CONCLUSION: The Spirulina maxima showed a hypolipemic effect, especially on the TAG and the LDL-C concentrations but indirectly on TC and HDL-C values. It also reduces systolic and diastolic blood pressure.

Publication Types:

- Clinical Trial
- Research Support, Non-U.S. Gov't

PMID: 18039384 [PubMed - indexed for MEDLINE]

Cardioprotective

Phytother Res. 2005 Dec;19(12):1030-7.

Protective effect of Spirulina against doxorubicin-induced cardiotoxicity.

Khan M, **Shobha JC**, **Mohan IK**, **Naidu MU**, **Sundaram C**, **Singh S**, **Kuppusamy P**, **Kutala VK**.

Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, India.

The generation of reactive oxygen species and mitochondrial dysfunction has been implicated in doxorubicin (DOX)-induced cardiotoxicity. The aim of the present study was to determine whether Spirulina, a blue-green algae, could serve as a cardioprotective agent during DOX treatment in a mouse model. Mice were treated with DOX (4 mg/kg bw, intraperitoneally), weekly, for 4 weeks. Spirulina was administered orally for 3 days twice daily, then for 7 weeks along with the four equal injections of DOX. Cardiotoxicity was assessed, at 3 weeks after the end of the DOX-treatment period, by mortality, volume of ascites, liver congestion, oxidative stress and ultrastructural changes of heart tissue. The DOX-treated animals showed higher mortality (53%) and more ascites. Myocardial damage, as assessed by ultrastructural changes, showed loss of myofibrils, cytoplasmic vacuolization and mitochondrial swelling. Myocardial superoxide dismutase and glutathione peroxidase activities were decreased and lipid peroxidation was increased. Pretreatment with Spirulina significantly protected the mice from DOX-induced cardiotoxic effects as evidenced from lower mortality (26%), less ascites, lower levels of lipid peroxidation, normalization of antioxidant enzymes and ultrastructural studies showing minimal damage to the heart. In vitro cytotoxic studies using ovarian cancer cells demonstrated that Spirulina did not compromise the anti-tumor activity of doxorubicin. These results suggest that Spirulina has a protective effect against cardiotoxicity induced by DOX and it may, therefore, improve the therapeutic index of DOX. Copyright 2005 John Wiley & Sons, Ltd.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 16372368 [PubMed - indexed for MEDLINE]

Cardioprotective

Am J Physiol Heart Circ Physiol. 2006 May;290(5):H2136-45. Epub 2005 Dec 22.

C-phycocyanin protects against ischemia-reperfusion injury of heart through involvement of p38 MAPK and ERK signaling.

Khan M, **Varadharaj S**, **Ganesan LP**, **Shobha JC**, **Naidu MU**, **Parinandi NL**, **Tridandapani S**, **Kutala VK**, **Kuppusamy P**.

Davis Heart and Lung Research Institute, Division of Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University, Columbus, OH 43210, USA.

We previously showed that C-phycocyanin (PC), an antioxidant biliprotein pigment of Spirulina platensis (a blue-green alga), effectively inhibited doxorubicin-induced oxidative stress and apoptosis in cardiomyocytes. Here we investigated the cardioprotective effect of PC against ischemia-reperfusion (I/R)-induced myocardial injury in an isolated perfused Langendorff heart model. Rat hearts were subjected to 30 min of global ischemia at 37 degrees C followed by 45 min of reperfusion. Hearts were perfused with PC (10 microM) or Spirulina preparation (SP, 50 mg/l) for 15 min before the onset of ischemia and throughout reperfusion. After 45 min of reperfusion, untreated (control) hearts showed a significant decrease in recovery of coronary flow (44%), left ventricular developed pressure (21%), and rate-pressure product (24%), an increase in release of lactate dehydrogenase and creatine kinase in coronary effluent, significant myocardial infarction (44% of risk area), and TdT-mediated dUTP nick end label-positive apoptotic cells compared with the preischemic state. PC or SP significantly enhanced recovery of heart function and decreased infarct size, attenuated lactate dehydrogenase and creatine kinase release, and suppressed I/R-induced free radical generation. PC reversed I/R-induced activation of p38 MAPK, Bax, and caspase-3, suppression of Bcl-2, and increase in TdT-mediated dUTP nick end label-positive apoptotic cells. However, I/R also induced activation of ERK1/2, which was enhanced by PC treatment. Overall, these results for the first time showed that PC attenuated I/R-induced cardiac dysfunction through its antioxidant and antiapoptotic actions and modulation of p38 MAPK and ERK1/2.

PMID: 16373583 [PubMed - indexed for MEDLINE]

Cardioprotective

J Nutr. 2005 Oct;135(10):2425-30.

A novel protein C-phycocyanin plays a crucial role in the hypocholesterolemic action of Spirulina platensis concentrate in rats.

Nagaoka S, **Shimizu K**, **Kaneko H**, **Shibayama F**, **Morikawa K**, **Kanamaru Y**, **Otsuka A**, **Hirahashi T**, **Kato T**.

Department of Applied Life Science, Faculty of Applied Biological Sciences, Gifu University, Gifu 501-1193, Japan. nagaoka@cc.gifu-u.ac.jp

This study was designed to clarify the mechanisms of the hypocholesterolemic action of Spirulina platensis concentrate (SPC) and identify the novel hypocholesterolemic protein derived from SPC. We investigated the effects of casein or SPC on the solubility of cholesterol, taurocholate binding capacity in vitro, cholesterol absorption in Caco-2 cells, and cholesterol metabolism in rats for 10 d. We also evaluated the effects of SPC, C-phycocyanin (PHY), and PHY residue on cholesterol metabolism in rats fed a high-cholesterol diet for 5 d, and SPC or SPC-acetone extract for 10 d. SPC had a significantly greater bile acid-binding capacity than casein in vitro. Micellar cholesterol solubility and cholesterol uptake by Caco-2 cells was significantly lower in the presence of SPC compared with casein. Fecal excretion of cholesterol and bile acids was significantly greater in rats fed the SPC-supplemented diet than in those fed the casein control diet. Serum and liver cholesterol concentrations were significantly lower in rats fed SPC than in those fed casein. Thus, the hypocholesterolemic action of SPC may involve the inhibition of both jejunal cholesterol absorption and ileal bile acid reabsorption. Although no studies to date have found a hypocholesterolemic protein among the algal proteins, we report here the discovery of a hypocholesterolemic effect in the novel protein C-phycocyanin. This study provides the first direct evidence that PHY, a novel hypocholesterolemic protein derived from Spirulina platensis, can powerfully influence serum cholesterol concentrations and impart a stronger hypocholesterolemic activity than SPC in animals.

Publication Types:

- In Vitro

PMID: 16177207 [PubMed - indexed for MEDLINE]

Cardioprotective

J Agric Food Chem. 2007 Sep 19;55(19):7962-7. Epub 2007 Aug 16.

Phycobiliprotein C-phycocyanin from Spirulina platensis is powerfully responsible for reducing oxidative stress and NADPH oxidase expression induced by an atherogenic diet in hamsters.

Riss J, **Décordé K**, **Sutra T**, **Delage M**, **Baccou JC**, **Jouy N**, **Brune JP**, **Oréal H**, **Cristol JP**, **Rouanet JM**.

EA 4188, Nutrition Humaine, Biodisponibilité et Athérogénèse, Place E. Bataillon, Université Montpellier 1 & 2, 34095 Montpellier, France.

The effects of spirulina and its chromophore phycocyanin, both without bound Se or selenium-enriched, were studied on plasma cholesterol, early atherosclerosis, cardiac production of superoxide anions, and NAD(P)H oxidase expression in hamsters. Forty hamsters were divided into 5 groups of 8 and fed an atherogenic diet for 12 weeks. They received by gavage either 7.14 mL/(kg day) phycocyanin (PC), Se-rich phycocyanin (SePC), spirulina (SP) or Se-rich spirulina (SeSP) in water, or water as control. SeSP and SePC supplied 0.4 microg of Se per 100 g body weight. Plasma cholesterol and non-HDL cholesterol concentrations were lower in group consuming SePC. HDL-cholesterol was never affected. SePC significantly increased plasma antioxidant capacity by 42% compared with controls. A sparing effect in liver glutathione peroxidase (87% on average) and superoxide dismutase (56% on average) activity was observed for all the groups compared to controls. Aortic fatty streak area was significantly reduced in the experimental groups, especially by PC (82%) and SePC (85%). Cardiac production of superoxide anion significantly decreased by approximately 46-76% in the four experimental groups and especially in SePC group (76%). The expression of p22phox subunit of NAD(P)H oxidase decreased by 34% after consumption of SePC. The results indicate that chronic consumption of Se-rich spirulina phycocyanin powerfully prevents the development of atherosclerosis. The underlying mechanism is related mainly to inhibiting pro-oxidant factors and at a lesser extent improving the serum lipid profile.

PMID: 17696484 [PubMed - indexed for MEDLINE]

Cardioprotective

J Cardiovasc Pharmacol. 2006 Jan;47(1):9-20.

C-phycocyanin ameliorates doxorubicin-induced oxidative stress and apoptosis in adult rat cardiomyocytes.

Khan M, **Varadharaj S**, **Shobha JC**, **Naidu MU**, **Parinandi NL**, **Kutala VK**, **Kuppusamy P**.

Center for Biomedical EPR Spectroscopy and Imaging, Davis Heart and Lung Research Institute, Department of Internal Medicine, The Ohio State University, Columbus, OH 43210, USA.

Doxorubicin (DOX), a potent antineoplastic agent, poses limitations for its therapeutic use due to the associated risk of developing cardiomyopathy and congestive heart failure. The cardiotoxicity of doxorubicin is associated with oxidative stress and apoptosis. We have recently shown that Spirulina, a blue-green alga with potent antioxidant properties, offered significant protection against doxorubicin-induced cardiotoxicity in mice. The aim of the present study was to establish the possible protective role of C-phycocyanin, one of the active ingredients of Spirulina, against doxorubicin-induced oxidative stress and apoptosis. The study was carried out using cardiomyocytes isolated from adult rat hearts. Doxorubicin significantly enhanced the formation of reactive oxygen species (ROS) in cells as measured by the 2',7'-dichlorodihydrofluorescein diacetate and dihydroethidium fluorescence. The doxorubicin-induced reactive oxygen species formation was significantly attenuated in cells pretreated with C-phycocyanin. It was further observed that the doxorubicin-induced DNA fragmentation and apoptosis, as assayed by TUNEL assay and flow cytometry coupled with BrdU-FITC/propidium iodide staining, were markedly attenuated by C-phycocyanin. C-phycocyanin also significantly attenuated the doxorubicin-induced increase in the expression of Bax protein, release of cytochrome c, and increase in the activity of caspase-3 in cells. In summary, C-phycocyanin ameliorated doxorubicin-induced oxidative stress and apoptosis in cardiomyocytes. This study further supports the crucial role of the antioxidant nature of C-phycocyanin in its cardioprotection against doxorubicin-induced oxidative stress and apoptosis.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 16424780 [PubMed - indexed for MEDLINE]

Cardioprotective

Vopr Pitan. 2003;72(6):28-31.

[Use of blue-green micro-seaweed Spirulina platensis for the correction of lipid and hemostatic disturbances in patients with ischemic heart disease]

[Article in Russian]

Ionov VA, **Basova MM**.

Changing in lipid spectrum, immunological state and coagulation in the 68 patients with IHD and atherogenic dyslipidemia who were taking biomass microalga Spirulina platensis was investigated. Modification of traditional plan of therapy of IHD when adding microalga Spirulina p. influences correcting effect to cascade procoagulation and immunopathological reactions, characteristic of atherosclerosis process.

Publication Types:

- Clinical Trial
- English Abstract

PMID: 14870586 [PubMed - indexed for MEDLINE]

Cardioprotective

Space Med Med Eng (Beijing). 2003 Jun;16(3):184-6.

[Effects of spirulina on serum lipids, erythrocyte membrane fluidity and vascular endothelial cells in tail-suspended rats]

[Article in Chinese]

Huang JM, **Bai SM**, **Hu ZX**, **Yang CL**, **Zhu DB**, **Shi JP**.

Objective: To study the changes of erythrocyte membrane fluidity, serum lipid and vascular endothelial cell caused by simulated weightlessness in rats and the beneficial effect of spirulina. Method: Thirty male SD rats were divided into 3 groups: free control group (group A) and two simulated weightlessness groups (groups B, C). Rats in group A and B were fed with normal forage, and the rats in group C were fed with normal forage supplemented with 5% (W/W) spirulina. Water was taken ad libitum. Result: Levels of serum CHO, HDL, TG, HDL-C/CHO and erythrocyte membrane fluidity decreased significantly, and number of vascular endothelial cells in plasma increased markedly in group B as compared with those in group A; The ratio of LDL-C/HDL-C, and atherosclerosis index (AI) decreased, number of vascular endothelial cells significantly lowered; level of CHO, HDL-C and value of the IDmax of plasma as well as erythrocyte membrane fluidity remarkedly increased in group C compared with those in group B. Conclusion: Spirulina can improve the physiological conditions of erythrocyte membrane fluidity, serum lipid and vascular endothelial cell caused by simulated weightlessness in rats.

Publication Types:

- English Abstract

PMID: 12934612 [PubMed - indexed for MEDLINE]

Cardioprotective

J AOAC Int. 2001 Nov-Dec;84(6):1708-14.

Fatty acid composition of Chlorella and Spirulina microalgae species.

Otleş S, **Pire R**.

Ege University, Department of Food Engineering, Izmir, Turkey.
otles@bornova.ege.edu.tr

Two New Age foods which contain high concentrations of whole food nutrients are the single-celled microalgae Chlorella and Spirulina. They are accepted as functional foods, which are defined as products derived from natural sources, whose consumption is likely to benefit human health and enhance performance. These foods are used as a supplement/ingredient or as a complete food to enhance the performance and state of the human body, or improve a specific bodily function. Functional foods are used mainly as products to nourish the human body after physical exertion or as a preventive measure against ailments. We determined the fatty acid compositions, particularly polyunsaturated fatty acid compositions, of Chlorella and Spirulina by capillary column-gas chromatography. The data obtained show that Spirulina contains unusually high levels of gamma-linolenic acid, an essential polyunsaturated fatty acid.

Publication Types:

- Comparative Study

PMID: 11767135 [PubMed - indexed for MEDLINE]

Cardioprotective

Nutr Sci Vitaminol (Tokyo). 1990 Apr;36(2):165-71.

Effects of Spirulina platensis on plasma lipoprotein lipase activity in fructose-induced hyperlipidemic rats.

Iwata K, **Inayama T**, **Kato T**.

Laboratory of Nutrition, Kagawa Nutrition College, Tokyo, Japan.

The effects of Spirulina platensis on lipoprotein lipase activity and hepatic triglyceride lipase activity in post-heparin plasma were studied in fructose-induced hyperlipidemic rats. Male Wistar rats aged 3 weeks old (body weight, 54 g) were fed on the high-fructose diet (68%) or the high-fructose diets containing Spirulina at the level of 5, 10, and 15%, respectively, for 4 weeks. The dietary hyperlipidemia caused by the high-fructose diet was improved by Spirulina feeding, accompanied by a significant increase in the lipoprotein lipase activity in post-heparin plasma.

PMID: 2117648 [PubMed - indexed for MEDLINE]

Cardioprotective

J Ethnopharmacol. 2001 Apr;75(1):37-44.

Effects of the ethanolic extract of Spirulina maxima on endothelium dependent vasomotor responses of rat aortic rings.

Paredes-Carbajal MC, **Torres-Durán PV**, **Díaz-Zagoya JC**, **Mascher D**, **Juárez-Oropeza MA**.

Department of Physiology, School of Medicine, UNAM, P.O. Box 70-250, Mexico D.F. 04510, Mexico. cparedes@servidor.unam.mx

Dietary Spirulina decreases, endothelium-dependently, the responses to vasoconstrictor agonists and increases the endothelium-dependent, agonist-induced, vasodilator responses of rat aorta rings. The aim of this study was to analyze, in vitro, the effects of a raw ethanolic extract of Spirulina maxima on the vasomotor responses of rat aortic rings to phenylephrine and to carbachol. On rings with endothelium, the extract produced the following effects: (a) a concentration-dependent (60-1000 microg/ml) decrease of the contractile response to phenylephrine; (b) a rightward shift and a decrease in maximal developed tension, of the concentration--response curve to phenylephrine; (c) a concentration dependent relaxation of phenylephrine-precontracted rings. These effects were blocked by L-NAME, and not modified by indomethacin. The extract had no effect on the concentration-response curve to carbachol of rings with endothelium. On endothelium-denuded rings the extract caused a significant rightward shift of the concentration response curve to phenylephrine without any effect on maximal tension development. In the presence of the extract, indomethacin induced a marked decrease in the maximal phenylephrine-induced tension of endothelium-denuded rings. These results suggest that the extract increases the basal synthesis/release of NO by the endothelium and, also, the synthesis/release of a cyclooxygenase-dependent vasoconstricting prostanoid by vascular smooth muscle cells.

Publication Types:

- In Vitro
- Research Support, Non-U.S. Gov't

PMID: 11282441 [PubMed - indexed for MEDLINE]

Cardioprotective

Life Sci. 1997;61(15):PL 211-9.

Effects of dietary Spirulina maxima on endothelium dependent vasomotor responses of rat aortic rings.

Paredes-Carbajal MC, Torres-Durán PV, Díaz-Zagoya JC, Mascher D, Juárez-Oropeza MA.

Department of Physiology, School of Medicine, UNAM, Mexico D.F., Mexico. majo@servidor.unam.mx

The aim of this study was to evaluate the effects of Spirulina maxima on vasomotor responses of aorta rings from male Wistar rats fed on a purified diet. For this purpose, the animals (weighing 200-240 g) were allocated randomly in two groups. One receiving purified control diet (A) and the other receiving purified diet containing 5% Spirulina (B). Purified diets were according to American Institute of Nutrition guidelines and adjusted to Spirulina protein content. All animals were fed (20 g/day/rat) during two weeks, receiving water ad libitum and 12 h. light-dark cycles. Spirulina maxima effects were evaluated by concentration-response (CR) curves of aorta rings with or without endothelium to phenylephrine (PE), both in presence and absence of indomethacin (Indom) or indomethacin plus L-NAME (Indom. + L-NAME), and to carbachol (CCh). Aorta rings with endothelium from group B showed, relative to corresponding rings from group A: 1) a significant decrease in the maximal tension developed in response to PE. 2) this decrease was reverted by Indom. 3) Indom. + L-NAME induced an additional increase in the contractile responses to PE. 4) a significant shift to the left of the CR curve to CCh. No significant differences were observed in the tension developed in response to PE in rings without endothelium from either group. These results suggest that Spirulina maxima may decrease vascular tone by increasing the synthesis and release of both a vasodilating cyclooxygenase-dependent product of arachidonic acid and nitric oxide, as well as by decreasing the synthesis and release of a vasoconstricting eicosanoid from the endothelial cells.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9328235 [PubMed - indexed for MEDLINE]

Cardioprotective

Arch Med Res. 2006 Jan;37(1):50-7.

Ethanolic extract of Spirulina maxima alters the vasomotor reactivity of aortic rings from obese rats.

Mascher D, Paredes-Carbajal MC, Torres-Durán PV, Zamora-González J, Díaz-Zagoya JC, Juárez-Oropeza MA.

Departamento de Fisiología, Universidad Nacional Autónoma de México, Mexico City, Mexico. mascher@servidor.unam.mx

BACKGROUND: Aortic rings with endothelium excised from fructose-fed obese rats develop more tension in response to phenylephrine and relax less in response to carbachol than corresponding rings from lean rats. This altered vascular reactivity is prevented when Spirulina maxima is added to the fructose-rich diet. In the present study the effects of a raw ethanolic extract of Spirulina maxima on the vasomotor responses of aorta rings from sucrose-fed obese hypertensive rats were analyzed. METHODS: The experiments were performed on aorta rings from sucrose-fed obese male rats. For each experiment, a pair of rings from the same aorta (one with intact endothelium, the other without a functional endothelium) was used. In this study we analyzed, in vitro, the effects of the ethanolic extract of Spirulina maxima on the reactivity of the aortic rings to phenylephrine and to carbachol. RESULTS: On rings with endothelium, the extract produced the following effects: a) a concentration-dependent (0.06-1.0 mg/mL) decrease of the contractile response to phenylephrine; b) a rightward shift and a decrease in maximal developed tension, of the concentration-response curve to phenylephrine; c) a concentration-dependent relaxation of phenylephrine-precontracted rings. These effects persisted in the presence of indomethacin but were prevented by L-NAME. The extract had no effect on the concentration-response curve of phenylephrine-precontracted rings to carbachol. On endothelium-denuded rings the extract caused a significant rightward shift of the concentration response curve to phenylephrine without any effect on maximal tension development. CONCLUSIONS: These results suggest that, in rings from obese rats, the extract, in addition to increasing the synthesis/release of NO, also inhibits the synthesis/release of a cyclooxygenase-dependent vasoconstrictor metabolite of arachidonic acid, which is increased in obesity.

Publication Types:

- In Vitro
- Research Support, Non-U.S. Gov't

PMID: 16314186 [PubMed - indexed for MEDLINE]

Cardioprotective

Planta Med. 2002 Jun;68(6):505-9.

Inhibition of cultured bovine aortic endothelial cell proliferation by sodium spirulan, a new sulfated polysaccharide isolated from Spirulina platensis.

Kaji T, **Fujiwara Y**, **Hamada C**, **Yamamoto C**, **Shimada S**, **Lee JB**, **Hayashi T**.

Department of Environmental Health, Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa, Japan. t-kaji@hokuriku-u.ac.jp

Sodium spirulan (Na-SP) is a sulfated polysaccharide isolated from the blue-green alga Spirulina platensis, which consists of two types of disaccharide repeating units, O-hexuronosyl-rhamnose (aldobiuronic acid) and O-rhamnosyl-3-O-methylrhamnose (acofriose) with sulfate groups, other minor saccharides and sodium ion. Vascular endothelial cells are present on the inner surface of blood vessels in a monolayer and have anticoagulant properties. To address the question whether Na-SP influences the maintenance of endothelial cell monolayers, we investigated the proliferation of cultured bovine aortic endothelial cells treated with Na-SP. It was found that Na-SP has an inhibitory activity on endothelial cell proliferation accompanied with suppression of whole protein synthesis but without non-specific cell damage. The inhibitory activity of Na-SP was the strongest when compared to that of heparan sulfate, heparin, dextran sulfate, dermatan sulfate, chondroitin sulfate A/C and hyaluronan. Furthermore, it was shown that the inhibitory activity of Na-SP disappeared by either desulfation or depolymerization. The present data suggest that Na-SP is a unique sulfated polysaccharide that strongly inhibits vascular endothelial cell proliferation, and the inhibitory activity requires polymerization of sulfated O-rhamnosyl-acofriose repeating units.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 12094292 [PubMed - indexed for MEDLINE]

Cardioprotective

Life Sci. 2004 Mar 26;74(19):2431-9.

Sodium spirulan as a potent inhibitor of arterial smooth muscle cell proliferation in vitro.

Kaji T, Okabe M, Shimada S, Yamamoto C, Fujiwara Y, Lee JB, Hayashi T.

Department of Environmental Health, Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3 Kanagawa-machi, Kanazawa 920-1181, Japan. t-kaji@hokuriku-u.ac.jp

Sodium spirulan (Na-SP) is a sulfated polysaccharide with M(r) approximately 220,000 isolated from the blue-green alga Spirulina platensis. The polysaccharide consists of two types of disaccharide repeating units, O-hexuronosyl-rhamnose (aldobiuronic acid) and O-rhamnosyl-3-O-methylrhamnose (acofriose) with sulfate groups, other minor saccharides and sodium ion. Since vascular smooth muscle cell proliferation is a crucial event in the progression of atherosclerosis, we investigated the effect of Na-SP on the proliferation of bovine arterial smooth muscle cells in culture. It was found that Na-SP markedly inhibits the proliferation without nonspecific cell damage. Either replacement of sodium ion with calcium ion or depolymerization of the Na-SP molecule to M(r) approximately 14,700 maintained the inhibitory activity, however, removal of sodium ion or desulfation markedly reduced the activity. Heparin and heparan sulfate also inhibited vascular smooth muscle cell growth but their effect was weaker than that of Na-SP; dextran sulfate, chondroitin sulfate, dermatan sulfate and hyaluronan failed to inhibit the cell growth. The present data suggest that Na-SP is a potent inhibitor of arterial smooth muscle cell proliferation, and the inhibitory effect requires a certain minimum sequence of polysaccharide structure whose molecular conformation is maintained by sodium ion bound to sulfate group.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 14998720 [PubMed - indexed for MEDLINE]

Cardioprotective

Yakugaku Zasshi. 2006 Jan;126(1):43-9.

[Isolation of pancreatic lipase activity-inhibitory component of spirulina platensis and it reduce postprandial triacylglycerolemia]

[Article in Japanese]

Han LK, **Li DX**, **Xiang L**, **Gong XJ**, **Kondo Y**, **Suzuki I**, **Okuda H**.

Department of Environmental and Symbiotic Sciences, Prefectural University of Kumamoto, Japan. hanlikun@hotmail.com

In the process of investigating the hypolipidemic effects of Spirulina platensis, we found that the aqueous extract of S. platensis may inhibit the intestinal absorption of dietary fat by inhibiting pancreatic lipase activity. The aqueous extract of S. platensis (500 m/kg) reduced the elevation of rat plasma triacylglycerol levels after oral administration of the lipid emulsion 2 h after administration. To clarify the hypolipidemic effects of S. platensis, the active component was isolated and designated 1'-O-(palmitonyl)-2'-O-(caprylonyl) glyceryl-beta-alpha-D-galactopyranoside (glycolipid H-b2). Glycolipid H-b2 was found to inhibit pancreatic lipase activity in a dose-dependent manner. The fractions containing glycolipid H-b2 (250 mg/kg) reduced the elevation of rat plasma triacylglycerol levels after oral administration of the lipid emulsion 2 h after administration. Furthermore, we examined the effects of phycocyanin isolated from S. platensis on pancreatic lipase activity. Phycocyanin inhibited the pancreatic lipase activity in a dose-dependent manner. These results suggest that the inhibitory effects of S. platensis on postprandial triacylglycerolemia may be due in part to the inhibition of pancreatic lipase activity by glycolipid H-b2 and phycocyanin.

Publication Types:

- English Abstract

PMID: 16394649 [PubMed - indexed for MEDLINE]

Cardioprotective

J Med Food. 2009 Feb;12(1):15-20.

Effects of dietary Spirulina on vascular reactivity.

Juárez-Oropeza MA, **Mascher D**, **Torres-Durán PV**, **Farias JM**, **Paredes-Carbajal MC**.

Departamento de Bioquímica, Facultad de Medicina, Universidad Nacional Autónoma de México, México DF, México. majo@servidor.unam.mx

There are several reports suggesting that Spirulina (Arthrospira) may have a beneficial effect in the prevention of cardiovascular diseases. Here we review the results of studies on the effects of dietary Spirulina on the vasomotor reactivity of aortic rings excised from either lean or obese Wistar rats. We also review preliminary results on the effects of Spirulina intake on plasma lipids and blood pressure in humans. The results of the former studies strongly suggest that Spirulina induces a tone-related increase in the synthesis/release of nitric oxide by the endothelium as well as an increase in the synthesis/release of a vasodilating cyclooxygenase-dependent metabolite of arachidonic acid and/or a decrease in the synthesis/release of a vasoconstricting eicosanoid by the endothelium. In humans, Spirulina maxima intake decreases blood pressure and plasma lipid concentrations, especially triacylglycerols and low-density lipoprotein-cholesterol, and indirectly modifies the total cholesterol and high-density lipoprotein-cholesterol values.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 19298191 [PubMed - in process]

Cardioprotective

Cardiovasc Hematol Agents Med Chem. 2008 Oct;6(4):237-52.

Medicinal agents in the metabolic syndrome.

Baños G, **Pérez-Torres I**, **El Hafidi M**.

Department of Biochemistry, National Institute of Cardiology Ignacio Chávez, Juan Badiano 1. Tlalpan. México D. F. 14080. México. gbanos@yahoo.com

The metabolic syndrome (MS) has become a worldwide health problem. It is difficult for patients to follow a diet/exercise regime that would improve their symptoms, therefore the investigation of agents that may deal with its more serious aspects is an important medical field for research. The cardiovascular consequences associated with the syndrome and some of the therapeutic approaches are discussed. The different agents can be divided into several groups: Inorganic/ organic: Zinc complexes with garlic components as insulino-mimetics; Selenium as antioxidant; Copper, Zinc and Manganese as microcomponents of antioxidant enzymes. Organic: Natural or Synthetic: Glycine is effective in lowering blood pressure, TBARS, intra-abdominal fat tissue and triglycerides in sucrose-fed rats. Pharmaceutical products: Fibrates, Lipid-lowering drugs. Antidiabetics. Anti-gout agents. On the other hand there are natural products such as those of animal origin: Sex hormones (also synthetic) used in the problems of menopause and hypoandrogenism frequently found in the MS, antioxidant Omega-3-oils (fish oils) or Vegetal: for example Digitalis pupurea, century-old cardiovascular medication as well as Magnolia officinalis; Spirulina maxima with beneficial effects as antioxidant and lipid-lowering agent, among others. Prickly Pear Cacti. (Opuntia Ficus- Indica Cochlospermum vitifolium (Willd.) Spreng) whose many properties against diabetes and hypercholesterolemia have been empirically known for many years. Perezone (from Perezia plants, a.k.a. Peonia) described as an antiplatelet aggregating agent. The mixed elements in the Mediterranean diet: Fish, salads (peppers, tomatoes), olive oil, garlic, red wine which combines fish oils, garlic and avocado as well as antioxidants from the rest of its components.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 18855636 [PubMed - indexed for MEDLINE]

Cardioprotective

Hepatoprotective

Med Hypotheses. 2009 Mar;72(3):330-2. Epub 2008 Sep 11.

Genistein and phycocyanobilin may prevent hepatic fibrosis by suppressing proliferation and activation of hepatic stellate cells.

McCarty MF, Barroso-Aranda J, Contreras F.

Oasis of Hope Hospital, Tijuana, Mexico. mccarty@pantox.com

Hepatic fibrosis reflects hepatotoxin-mediated activation of hepatic stellate cells, resulting in their proliferation and transformation to myofibroblasts that secrete collagen. This activation is suppressed by estrogen, an effect which explains the decreased risk for hepatic fibrosis enjoyed by premenopausal women and by postmenopausal women receiving hormone replacement therapy. Since stellate cells have been found to express the beta but not the alpha isoform of the estrogen receptor, it can be predicted that nutritional intakes of the soy isoflavone genistein - a selective agonist for ERbeta in the low nanomolar plasma concentrations achievable with these intakes - have potential for suppressing hepatic fibrosis, in both men and women. The antiproliferative impact of estrogen on stellate cells is mediated at least in part by suppression of NADPH oxidase activity; oxidant production by this enzyme complex plays a crucial role in stellate cell activation. Alternatively, it may be feasible to inhibit NADPH oxidase with phycocyanobilin (PCB), a biliverdin homolog found in spirulina that has recently been shown to inhibit the NADPH oxidase activity of human cell cultures in low micromolar concentrations. Joint administration of soy isoflavones and PCB in appropriate doses might have considerable potential for prevention of hepatic fibrosis in at-risk subjects.

PMID: 18789597 [PubMed - indexed for MEDLINE]

Lik Sprava. 2000 Sep;(6):89-93.

[Clinical and experimental study of spirulina efficacy in chronic diffuse liver diseases]

[Article in Ukrainian]

Gorban' EM, **Orynchak MA**, **Virstiuk NG**, **Kuprash LP**, **Panteleĭmonova TM**, **Sharabura LB**.

The results of examination of 60 patients presenting with chronic diffuse disorders of the liver and seventy experimental animals with toxic affection of the liver, having been administered spirulina treatments, suggest clinical-and-laboratory effectiveness of this drug. The hepatoprotective properties of spirulina are referrable to its antiinflammatory, antioxidant, membrane-stabilizing, and immunocorrecting actions. In this way the employment of spirulina is believed to be pathogenetically validated in chronic diffuse liver conditions, permitting stabilizing the process and preventing the transformation of chronic hepatitis into hepatocirrhosis.

Publication Types:

- English Abstract

PMID: 11455931 [PubMed - indexed for MEDLINE]

Hepatoprotective

Biochem Biophys Res Commun. 1998 Aug 19;249(2):428-31.

Hepatoprotective effect of C-phycocyanin: protection for carbon tetrachloride and R-(+)-pulegone-mediated hepatotoxicty in rats.

Vadiraja BB, **Gaikwad NW**, **Madyastha KM**.

Department of Organic Chemistry, Indian Institute of Science, Bangalore, 560 012, India.

Effect of C-phycocyanin (from Spirulina platensis) pretreatment on carbontetrachloride and R-(+)-pulegone-induced hepatotoxicity in rats was studied. Intraperitoneal (i.p.) administration (200 mg/kg) of a single dose of phycocyanin to rats, one or three hours prior to R-(+)-pulegone (250 mg/kg) or carbontetrachloride (0.6 ml/kg) challenge, significantly reduced the hepatotoxicity caused by these chemicals. For instance, serum glutamate pyruvate transaminase (SGPT) activity was almost equal to control values. The losses of microsomal cytochrome P450, glucose-6-phosphatase and aminopyrine-N-demethylase were significantly reduced, suggesting that phycocyanin provides protection to liver enzymes. It was noticed that the level of menthofuran, the proximate toxin of R-(+)-pulegone was nearly 70% more in the urine samples collected from rats treated with R-(+)-pulegone alone than rats treated with the combination of phycocyanin and R-(+)-pulegone. The possible mechanism involved in the hepatoprotection is discussed.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9712713 [PubMed - indexed for MEDLINE]

Hepatol Res. 2008 May;38(5):511-20. Epub 2007 Nov 21.

C-Phycocyanin ameliorates 2-acetylaminofluorene induced oxidative stress and MDR1 expression in the liver of albino mice.

Roy KR, Nishanth RP, Sreekanth D, Reddy GV, Reddanna P.

Department of Animal Sciences, School of Life Sciences, University of Hyderabad, Hyderabad, India.

Aim: To study the effect of C-Phycocyanin (C-PC), a biliprotein isolated from Spirulina platensis, on 2-acetylaminofluorene (2-AAF) induced oxidative stress and MDR1 expression in the liver of albino mice. Methods: In the present study, albino mice aged 40-60 days were used. The mice were randomly assigned to four groups of six animals each. The first group was treated with the vehicle (absolute alcohol), the second group was treated with C-PC (50 mg/kg body weight), the third group was treated with 2-AAF (25 mg/kg body weight) and the fourth group was treated with C-PC (50 mg/kg body weight) and 2-AAF, daily for 3 days. The mice were sacrificed and the tissues were collected and stored for histology and biochemical studies. Results: 2-AAF induced liver tissue damage in albino mice. 2-AAF treatment resulted in upregulation of MDR1 expression and enhanced the generation of reactive oxygen species (ROS). It also induced phosphorylation of Akt and nuclear translocation of NF-kappaB. Co-administration of C-PC and 2-AAF inhibited the expression of MDR1 by preventing ROS generation, Akt phosphorylation and NF-kappaB nuclear translocation. Conclusion: 2-AAF-induced oxidative stress is reduced by C-PC treatment. C-PC inhibited the 2-AAF induced expression of MDR1 by interfering at the level of ROS generation, Akt phosphorylation and NF-kappaB translocation. This study reveals the usefulness of C-PC in preventing oxidative stress and downregulation of MDR1 induced by xenobiotics like 2-AAF.

PMID: 18034828 [PubMed - in process]

Hepatoprotective

J Ethnopharmacol. 1999 Feb;64(2):141-7.

Studies on the preventive effect of Spirulina maxima on fatty liver development induced by carbon tetrachloride, in the rat.

Torres-Durán PV, **Miranda-Zamora R**, **Paredes-Carbajal MC**, **Mascher D**, **Blé-Castillo J**, **Díaz-Zagoya JC**, **Juárez-Oropeza MA**.

Department of Biochemistry, School of Medicine, UNAM, Mexico D.F., Mexico.

The aim of the present work was to assess if the feeding of either the oil extract of Spirulina maxima or of its defatted fraction would prevent fatty liver development, induced in rats by a single intraperitoneal dose of carbon tetrachloride (CCl4). Liver and serum lipids were evaluated 4 days after treatment with this agent. Concentration of liver lipids did not differ in rats fed on a purified diet either without or with one of the fractions of Spirulina, except for total cholesterol, which showed a slight increase in the group receiving the oil extract of Spirulina. However, after CCl4 treatment, liver total lipids and triacylglycerols were significantly lower in rats fed on a diet containing any fraction of Spirulina (defatted or the oil fraction) than in rats without Spirulina in their diet. Furthermore, the increased liver cholesterol values, induced by CCl4 treatment, were not observed in rats receiving Spirulina. In addition, rats receiving whole Spirulina in their diet and treated only with the vehicle showed an increase in the percentage of HDL values. The changes in VLDL and LDL induced by CCl4 treatment were not observed in the whole Spirulina group. Furthermore, after CCl4 treatment the values of the liver microsomal thiobarbituric acid-reactive substances were lower in the whole Spirulina group than in the control group. These results support the potential hepatoprotective role of Spirulina.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 10197749 [PubMed - indexed for MEDLINE]

Hepatoprotective

Biochem Mol Biol Int. 1998 Apr;44(4):787-93.

Spirulina maxima prevents induction of fatty liver by carbon tetrachloride in the rat.

Torres-Durán PV, **Miranda-Zamora R**, **Paredes-Carbajal MC**, **Mascher D**, **Díaz-Zagoya JC**, **Juárez-Oropeza MA**.

Departamento de Bioquímica, UNAM, México, D.F., Mexico.

The aim of the present work was to assess the capacity of Spirulina maxima to prevent fatty liver development induced in rats by an intraperitoneal single dose (1 ml/kg) of carbon tetrachloride. Liver and serum lipids were quantified two or four days after treatment with this agent. Liver lipid concentration did not differ in rats fed on a purified diet with or without Spirulina. However, after carbon tetrachloride treatment, liver triacylglycerols were significantly lower in rats fed on a diet with Spirulina 5% than in rats without Spirulina in their diet ($P < 0.05$). Furthermore, the increased liver cholesterol values, induced by carbon tetrachloride treatment, were not observed in rats that received Spirulina. These results support the potential hepatoprotective role of Spirulina.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9584992 [PubMed - indexed for MEDLINE]

Hepatoprotective

Life Sci. 2002 Apr 19;70(22):2665-73.

Arthrospira maxima prevents the acute fatty liver induced by the administration of simvastatin, ethanol and a hypercholesterolemic diet to mice.

Blé-Castillo JL, **Rodríguez-Hernández A**, **Miranda-Zamora R**, **Juárez-Oropeza MA**, **Díaz-Zagoya JC**.

Laboratorio de Análisis Clínicos, Hospital General de Zona No. 1, Instituto Mexicano de Seguro Social, Villahermosa, Tabasco.

An evident fatty liver, corroborated morphologically and chemically, was produced in CD-1 mice after five daily doses of simvastatin 75 mg/Kg body weight, a hypercholesterolemic diet and 20 percent ethanol in the drinking water. After treating the animals, they presented serum triacylglycerols levels five times higher than the control mice, total lipids, cholesterol and triacylglycerols in the liver were 2, 2 and 1.5 times higher, respectively, than in control animals. When Arthrospira maxima was given with diet two weeks prior the onset of fatty liver induction, there was a decrement of liver total lipids (40%), liver triacylglycerols (50%) and serum triacylglycerols (50%) compared to the animals with the same treatment but without Arthrospira maxima. In addition to the mentioned protective effect, the administration of this algae, produced a significant increase (45%) in serum high density lipoproteins. The mechanism for this protective effect was not established in these experiments.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 12269393 [PubMed - indexed for MEDLINE]

Hepatoprotective

Life Sci. 1993;53(1):57-61.

Preventive effect of Spirulina maxima on the fatty liver induced by a fructose-rich diet in the rat, a preliminary report.

González de Rivera C, Miranda-Zamora R, Díaz-Zagoya JC, Juárez-Oropeza MA.

Departamento de Bioquímica, Facultad de Medicina, UNAM, México, D.F.

Cyanobacteria Spirulina maxima from Texcoco Lake in Mexico was administered as a 5% component of a purified diet, to Wistar rats together with a high percentage of fructose (60%) and its effect on several lipid fractions of plasma and liver was studied and compared to those of rats fed purified diets containing 60% of glucose or 60% of fructose. A preventive effect of Spirulina maxima on the fructose-induced increase of the liver triglycerides level was observed together with an elevation of the phospholipid concentration in this tissue. On the other hand Spirulina maxima produced a plasma cholesterol level even lower than that observed in the control group.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 8515682 [PubMed - indexed for MEDLINE]

Hepatoprotective

Wei Sheng Yan Jiu. 2007 Jan;36(1):34-6.

[Antagonistic effects of Se-rich Spirulina platensis on rat liver fibrosis]

[Article in Chinese]

Huang Z, **Zheng W**.

College of Life Science and Technology, Ji'nan University,Guangzhou 510632, China. tzhwj@jnu.edu.cn

OBJECTIVE: Antagonistic effects of supplement of Se-rich Spirulina platensis (Se-SP) on hepatocirrhosis were investigated with the rat model of liver fibrosis induced by intraperitoneal injection 3% thioacetamide (TAA). METHODS: Parameters of routine liver function, content of malondialdehyde (MDA) and activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD) in rat serum were determined by colorimetry. Content of selenium (Se) was measured by DAN fluorometry method and hyaluronic acid (HA) was detected by radio-immunoassay. Liver fibrosis was diagnosed by HE staining and relative contents of collagen (RCC) were estimated by Masson's trichrome staining. RESULTS: Parameters of liver function in Se-SP group were most recovered in all protective groups. Compared with the model groups, contents of MDA and HA were lower, whereas activities of GPx and SOD were higher ($P < 0.05$) in rats serum of Se-SP group. The RCC in rats liver of Se-SP group were lower than those of the model groups, where the liver fibrosis were identified dominantly to degree I according to pathological diagnosis. Moreover, Se content in rats serum had positive correlation ($r = 0.645$) with activity of GPx while a negative correlation ($r = 0.675$) with MDA level. CONCLUSION: The results indicated that Se-SP have detectable antagonistic effects to liver fibrosis, and suggested that enhancement of antioxidation level and liver reserve function might be associated with these effects.

Publication Types:

- English Abstract

PMID: 17424844 [PubMed - in process]

Hepatoprotective

Renal Protective

Fundam Clin Pharmacol. 2006 Apr;20(2):121-8.

Effect of Spirulina, a blue green algae, on gentamicin-induced oxidative stress and renal dysfunction in rats.

Kuhad A, **Tirkey N**, **Pilkhwal S**, **Chopra K**.

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh 160014, India.

Gentamicin (GM), an aminoglycoside, is widely employed in clinical practice for the treatment of serious Gram-negative infections. The clinical utility of GM is limited by the frequent incidence of acute renal failure. Experimental evidences suggest that oxidative and nitrosative stress play an important role in GM nephrotoxicity. Spirulina fusiformis is a blue green algae with potent free radical scavenging properties. The present study was designed to investigate renoprotective potential of S. fusiformis, against GM-induced oxidative stress and renal dysfunction. Spirulina fusiformis (500, 1000, 1500 mg/kg, p.o.) was administered 2 days before and 8 days concurrently with GM (100 mg/kg, i.p.). Renal injury was assessed by measuring serum creatinine, blood urea nitrogen and creatinine clearance and serum nitrite levels. Renal oxidative stress was determined by renal malondialdehyde levels, reduced glutathione levels and by enzymatic activity of superoxide dismutase (SOD) and catalase. Chronic GM administration resulted in marked renal oxidative and nitrosative stress and significantly deranged renal functions. Treatment with S. fusiformis significantly and dose-dependently restored renal functions, reduced lipid peroxidation and enhanced reduced glutathione levels, SOD and catalase activities. The results of present study clearly demonstrate the pivotal role of reactive oxygen species and their relation to renal dysfunction and point to the therapeutic potential of S. fusiformis in GM-induced nephrotoxicity.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16573712 [PubMed - indexed for MEDLINE]

Clin Chim Acta. 2004 Oct;348(1-2):199-205.

Salubrious effect of C-phycocyanin against oxalate-mediated renal cell injury.

Farooq SM, Asokan D, Sakthivel R, Kalaiselvi P, Varalakshmi P.

Department of Medical Biochemistry, Dr. AL Mudaliar Post-Graduate Institute of Basic Medical Sciences, University of Madras, Taramani, Chennai-600 113, India.

BACKGROUND: C-phycocyanin, a biliprotein pigment found in some blue green algae (Spirulina platensis) with nutritional and medicinal properties, was investigated for its efficacy on sodium oxalate-induced nephrotoxicity in experimentally induced urolithic rats. METHODS: Male Wistar rats were divided into four groups. Hyperoxaluria was induced in two of these groups by intraperitoneal infusion of sodium oxalate (70 mg/kg), and a pretreatment of phycocyanin (100 mg/kg) as a single oral dosage was given to one of these groups by 1 h prior to sodium oxalate infusion challenges. The study also encompasses an untreated control group and a phycocyanin-alone treated drug control group. The extent of lipid peroxidation (LPO) was evaluated in terms of renal concentrations of MDA, conjugated diene and hydroperoxides. The following assay was performed in the renal tissue (a) antioxidant enzymes such as superoxide dismutase (SOD) and catalase, (b) glutathione metabolizing enzymes such as glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) and glucose 6-phosphate dehydrogenase (G6PD), (c) the low molecular weight antioxidants (GSH, vitamins E and C) and protein carbonyl content. RESULTS: The increased concentrations of MDA, conjugated diene and hydroperoxide (index of the lipid peroxidation) were controlled ($P < 0.001$) in the phycocyanin-pretreated group. At the outset, the low molecular weight antioxidants were appreciably increased ($P < 0.001$), whereas the tissue protein carbonyl concentration was decreased ($P < 0.001$), suggesting that phycocyanin provides protection to renal cell antioxidants. It was noticed that the activities of antioxidant enzymes and glutathione metabolizing enzymes were considerably stabilized in rats pretreated with phycocyanin. CONCLUSION: We suggest that phycocyanin protects the integrity of the renal cell by stabilizing the free radical mediated LPO and protein carbonyl, as well as low molecular weight antioxidants and antioxidant enzymes in renal cells. Thus, the present analysis reveals that the antioxidant nature of C-phycocyanin protects the renal cell against oxalate-induced injury and may be a nephroprotective agent.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 15369755 [PubMed - indexed for MEDLINE]

Renal Protective

Chem Biol Interact. 2004 Aug 10;149(1):1-7.

Prophylactic role of phycocyanin: a study of oxalate mediated renal cell injury.

Farooq SM, Asokan D, Kalaiselvi P, Sakthivel R, Varalakshmi P.

Department of Medical Biochemistry, Dr. ALM Postgraduate Institute of Basic Medical Sciences, University of Madras, Taramani, Chennai 600113, India.

Oxalate induced renal calculi formation and the associated renal injury is thought to be caused by free radical mediated mechanisms. An in vivo model was used to investigate the effect of phycocyanin (from Spirulina platensis), a known antioxidant, against calcium oxalate urolithiasis. Male Wistar rats were divided into four groups. Hyperoxaluria was induced in two of these groups by intraperitoneal infusion of sodium oxalate (70 mg/kg) and a pretreatment of phycocyanin (100 mg/kg) as a single oral dosage was given, 1h prior to sodium oxalate infusion. An untreated control and drug control (phycocyanin alone) were also included in the study. We observed that phycocyanin significantly controlled the early biochemical changes in calcium oxalate stone formation. The antiurolithic nature of the drug was evaluated by the assessment of urinary risk factors and light microscopic observation of urinary crystals. Renal tubular damage as divulged by urinary marker enzymes (alkaline phosphatase, acid phosphatase and gamma-glutamyl transferase) and histopathological observations such as decreased tubulointerstitial, tubular dilatation and mononuclear inflammatory cells, indicated that renal damage was minimised in drug-pretreated group. Oxalate levels ($P < 0.001$) and lipid peroxidation ($P < 0.001$) in kidney tissue were significantly controlled by drug pretreatment, suggesting the ability of phycocyanin to quench the free radicals, thereby preventing the lipid peroxidation mediated tissue damage and oxalate entry. This accounts for the prevention of CaOx stones. Thus, the present analysis revealed the antioxidant and antiurolithic potential of phycocyanin thereby projecting it as a promising therapeutic agent against renal cell injury associated kidney stone formation.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15294440 [PubMed - indexed for MEDLINE]

Renal Protective

Mol Cell Biochem. 2006 Mar;284(1-2):95-101. Epub 2006 Feb 14.

Oxalate mediated nephronal impairment and its inhibition by c-phycocyanin: a study on urolithic rats.

Farooq SM, Ebrahim AS, Subramhanya KH, Sakthivel R, Rajesh NG, Varalakshmi P.

Department of Medical Biochemistry, Dr. A.L.M. Postgraduate Institute of Basic Medical, Sciences, University of Madras, Taramani, Chennai, 600 113, India.

The assumption of oxidative stress as a mechanism in oxalate induced renal damage suggests that antioxidants might play a beneficial role against oxalate toxicity. An in vivo model was used to investigate the effect of C-phycocyanin (from aquatic micro algae; Spirulina spp.), a known antioxidant, against calcium oxalate urolithiasis. Hyperoxaluria was induced in two of the 4 groups of Wistar albino rats (n = 6 in each) by intraperitoneally injecting sodium oxalate (70 mg/kg body weight). A pretreatment of phycocyanin (100 mg/kg body weight) as a single oral dosage was given, one hour prior to oxalate challenge. An untreated control and drug control (phycocyanin alone) were employed. Phycocyanin administration resulted in a significant improvement ($p < 0.001$) in the thiol content of renal tissue and RBC lysate via increasing glutathione and reducing malondialdehyde levels in the plasma of oxalate induced rats ($p < 0.001$), indicating phycocyanin's antioxidant effect on oxalate mediated oxidative stress. Administering phycocyanin after oxalate treatment significantly increased catalase and glucose-6-phosphate dehydrogenase activity ($p < 0.001$) in RBC lysate suggesting phycocyanin as a free radical quencher. Assessing calcium oxalate crystal retention in renal tissue using polarization microscopy and renal ultrastructure by electron microscopy reveals normal features in phycocyanin--pretreated groups. Thus the study presents positive pharmacological implications of phycocyanin against oxalate mediated nephronal impairment and warrants further work to tap this potential aquatic resource for its medicinal application.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16477383 [PubMed - indexed for MEDLINE]

Renal Protective

Food Chem Toxicol. 2007 Jun;45(6):879-87. Epub 2006 Nov 23.

Evaluation of protective efficacy of Spirulina fusiformis against mercury induced nephrotoxicity in Swiss albino mice.

Sharma MK, **Sharma A**, **Kumar A**, **Kumar M**.

Department of Zoology, University of Rajasthan, Jaipur 302004, India.
mkshrma@hotmail.com

The toxicity of mercury to animals and man is well established and this depends greatly on the form of the mercury compounds. In most animals' species, including man, the kidney is the main site of deposition of inorganic mercury and target organ for its toxicity. In the present study Spirulina fusiformis (a cyanobacterium, belongs to family--Oscillatoriaceae) has been investigated as a possible modifier of mercury induced renal damages in Swiss albino mice. Animals were divided into four groups. (i) Control group--only vehicle (0.9% NaCl) was administered as i.p. (ii) HgCl(2) treated group--5.0 mg/kg b.wt. HgCl(2) was administered as i.p. (iii) Spirulina treated group--800 mg/kg b.wt. Spirulina extract was administered orally. (iv) Combination group--S. fusiformis was administered 10 days before mercuric chloride administration and continued upto 30 days after mercuric chloride administration (5.0 mg/kg b.wt.). The animals were autopsied on 1, 3, 7, 15 and 30 days after treatment and the activity of alkaline phosphatase (ALP), acid phosphatase (ACP), lactate dehydrogenase (LDH) and MDA (malondialdehyde) level were measured in kidney homogenates. The results indicated that there was a time-dependent significant enhancement in MDA content and ACP activity and decrease in LDH and ALP activity observed after HgCl(2) treatment. Mercury intoxication also induces pathological alterations in the kidney such as degeneration of glomerulus, proximal and distal tubules. A dose-dependent mortality was also observed following administration of different doses of HgCl(2). In combined treatment of Spirulina with HgCl(2), a significant decrease in MDA content and ACP activity and elevation in LDH and ALP activity was observed as compared to HgCl(2) treated group. Spirulina pre- and post-treatment with mercury also significantly reduces pathological alterations in kidney. Thus, the results from the present study suggest that S. fusiformis can significantly modify the renal damages against mercuric chloride induced toxicity.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17215067 [PubMed - indexed for MEDLINE]

Renal Protective

J Appl Toxicol. 2006 Sep-Oct;26(5):444-51.

Spirulina attenuates cyclosporine-induced nephrotoxicity in rats.

Khan M, **Shobha JC**, **Mohan IK**, **Rao Naidu MU**, **Prayag A**, **Kutala VK**.

Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad 500 082, India.

Cyclosporine (CsA) causes a dose-related decrease in renal function in experimental animals and humans. The generation of reactive oxygen species (ROS) has been implicated in CsA-induced nephrotoxicity. It was previously shown that Spirulina, a blue-green algae, with antioxidant properties effectively attenuated the doxorubicin-induced cardiotoxicity in mice and cisplatin-induced nephrotoxicity in rat. The present study investigated the nephroprotective role of Spirulina against CsA-induced nephrotoxicity in rats. Spirulina (500 mg kg(-1) b.w.) was administered orally for 3 days before and 14 days concurrently with CsA (50 mg kg-1 b.w.). Rats treated with CsA showed nephrotoxicity as evidenced from a significant elevation in plasma urea, creatinine, urinary N-acetyl-beta-D-glucosaminidase (beta-NAG) and a decrease in creatinine and lithium clearance. Pretreatment with Spirulina protected the rats from CsA-induced nephrotoxicity. The CsA-induced rise in plasma urea and creatinine and the decrease in creatinine and lithium clearance were attenuated by Spirulina. There was a significant increase in plasma and kidney tissue MDA with CsA. Spirulina prevented the rise in plasma and kidney tissue MDA. Histopathology of the kidney from CsA-treated rats showed severe isometric vacuolization and widening of the interstitium. However, pretreatment with Spirulina prevented such changes, and the kidney morphology was comparable to that of the control. Spirulina treatment did not alter the blood CsA levels. These results suggest that Spirulina has a protective effect against nephrotoxicity induced by CsA. This study further supports the crucial role of the antioxidant nature of Spirulina in protecting against CsA-induced oxidative stress. Copyright 2006 John Wiley & Sons, Ltd.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16858688 [PubMed - indexed for MEDLINE]

Renal Protective

Ren Fail. 2006;28(3):247-54.

Renoprotective effect of Spirulina fusiformis on cisplatin-induced oxidative stress and renal dysfunction in rats.

Kuhad A, **Tirkey N**, **Pilkhwal S**, **Chopra K**.

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India.

Cisplatin is an effective chemotherapeutic agent used in the treatment of a wide array of both pediatric and adult malignancies. Dose-dependent and cumulative nephrotoxicity is the major toxicity of this compound, sometimes requiring a reduction in dose or discontinuation of treatment. Recent evidences have implicated oxidative and nitrosative stress in cisplatin-induced nephrotoxicity. Spirulina fusiformis, blue-green algae, is claimed to be a potential antioxidant. The present study was designed to explore the renoprotective potential of Spirulina fusiformis against cisplatin-induced oxidative stress and renal dysfunction. Spirulina fusiformis (500,1000,1500 mg/kg(-1) p.o.) was administered 2 days before and until 3 days after cisplatin challenge (5 mg/kg(-1) i.p.). Renal injury was assessed by measuring serum creatinine, blood urea nitrogen, creatinine and urea clearance, and serum nitrite levels. Renal oxidative stress was determined by renal TBARS levels, reduced glutathione levels, and by enzymatic activity of superoxide dismutase and catalase. A single dose of cisplatin produced marked renal oxidative and nitrosative stress and significantly deranged renal functions. Chronic Spirulina fusiformis treatment significantly and dose-dependently restored renal functions, reduced lipid peroxidation, and enhanced reduced glutathione levels, superoxide dismutase, and catalase activities. The results of the present study clearly demonstrate the pivotal role of reactive oxygen species and their relation to renal dysfunction and point to the therapeutic potential of Spirulina fusiformis in cisplatin-induced nephrotoxicity.

PMID: 16703798 [PubMed - indexed for MEDLINE]

Renal Protective

Cancer Chemother Pharmacol. 2006 Dec;58(6):802-8. Epub 2006 Mar 22.

Protection against cisplatin-induced nephrotoxicity by Spirulina in rats.

Mohan IK, **Khan M**, **Shobha JC**, **Naidu MU**, **Prayag A**, **Kuppusamy P**, **Kutala VK**.

Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, 500 082, Hyderabad, India.

PURPOSE: Cisplatin (CP)-induced nephrotoxicity is associated with the increased generation of reactive oxygen metabolites and lipid peroxidation in kidney, caused by the decreased levels of antioxidants and antioxidant enzymes. The purpose of this study was to evaluate the role of Spirulina, blue-green alga with antioxidant properties, in the protection of cisplatin-induced nephrotoxicity in rat. METHODS: Rats were treated with CP (6 mg/kg bw, single dose, intraperitoneally). Spirulina (1,000 mg/kg) was administered orally for 8 days and CP treatment was given on day 4. Nephrotoxicity was assessed, 6 days after the CP treatment, by measuring plasma urea, creatinine, urinary N-acetyl-(D-glucose-aminidase) (beta-NAG) and histopathology of kidney. RESULTS: Rats treated with CP showed marked nephrotoxicity as evidenced from the significant elevation in plasma urea, creatinine and urinary beta-NAG. Histological assessment revealed marked proximal tubular necrosis and extensive epithelial vacuolization in the kidney of CP-treated rats. Superoxide dismutase, catalase and glutathione peroxidase were decreased and lipid peroxidation was increased in kidney tissue. Pretreatment with Spirulina protected the rats from CP-induced nephrotoxicity. The rise in plasma urea, creatinine, urinary beta-NAG, plasma and kidney tissue MDA and histomorphological changes were significantly attenuated by Spirulina. In vitro studies using human ovarian cancer cells revealed that Spirulina did not interfere with the cytotoxic effects of CP on tumor cells. CONCLUSIONS: In summary, Spirulina significantly protected the CP-induced nephrotoxicity through its antioxidant properties.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 16552571 [PubMed - indexed for MEDLINE]

Renal Protective

Bosn J Basic Med Sci. 2008 Nov;8(4):331-6.

Spirulina platensis protects against renal injury in rats with gentamicin-induced acute tubular necrosis.

Avdagić N, **Cosović E**, **Nakas-Ićindić E**, **Mornjaković Z**, **Zaciragić A**, **Hadzović-Dzuvo A**.

Faculty of Medicine, Institute of Physiology and Biochemistry, University of Sarajevo, Sarajevo, Bosnia and Herzegovina.

The present study was carried out to evaluate the renoprotective antioxidant effect of Spirulina platensis on gentamicin-induced acute tubular necrosis in rats. Albino-Wistar rats, (9male and 9 female), weighing approximately 250 g, were used for this study. Rats were randomly assigned to three equal groups. Control group received 0,9 % sodium chloride intraperitoneally for 7 days at the same volume as gentamicin group. Gentamicin group was treated intraperitoneally with gentamicin, 80 mg/kg daily for 7 days. Gentamicin+spirulina group received Spirulina platensis 1000 mg/kg orally 2 days before and 7 days concurrently with gentamicin (80 mg/kg i.p.). Nephrotoxicity was assessed by measuring plasma nitrite concentration, stabile metabolic product of nitric oxide with oxygen. Plasma nitrite concentration was determined by colorimetric method using Griess reaction. For histological analysis kidney specimens were stained with hematoxylin-eosin (HE) and periodic acid-Schiff (PAS) stain. Plasma nitrite concentration and the level of kidney damage were significantly higher in gentamicin group in comparison both to the control and gentamicin+spirulina group. Spirulina platensis significantly lowered the plasma nitrite level and attenuated histomorphological changes related to renal injury caused by gentamicin. Thus, the results from present study suggest that Spirulina platensis has renoprotective potential in gentamicin-induced acute tubular necrosis possibly due to its antioxidant properties.

PMID: 19125703 [PubMed - indexed for MEDLINE]

Renal Protective

Phytother Res. 2008 Nov;22(11):1506-10.

Spirulina platensis protects against gentamicin-induced nephrotoxicity in rats.

Karadeniz A, **Yildirim A**, **Simsek N**, **Kalkan Y**, **Celebi F**.

Department of Physiology, Faculty of Veterinary Medicine, Atatürk University, Erzurum, Turkey. karadenizali@atauni.edu.tr

The present study aimed to investigate the protective effect of Spirulina platensis (SP) on gentamicin sulphate (GS)-induced changes in the levels of lipid peroxidation and endogenous antioxidants in the kidney of rats. Sprague-Dawley rats were treated in separate groups as follows for 7 consecutive days: control (C), gentamicin sulphate (100 mg/kg i.p.) (GS), Spirulina platensis (1000 mg/kg orally) (SP) and Spirulina platensis (1000 mg/kg orally) plus gentamicin sulphate (100 mg/kg i.p.) (SP + GS). The degree of protection was evaluated by determining the effects of Spirulina platensis on malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GPX) and nitric oxide (NO), and plasma creatinine and urea levels were estimated in kidney homogenates to evaluate antioxidant activity, and the kidney was histologically examined as well. Spirulina platensis elicited significant nephroprotective activity by decreasing lipid peroxidation (MDA) and elevated the levels of GSH, SOD, GPX, NO, creatinine and urea. Furthermore, these biochemical observations were supplemented by histological examination of the rat kidneys. In conclusion, the present study indicates a very important role of reactive oxygen species (ROS) and the relation to renal dysfunction and point to the therapeutic potential of Spirulina platensis in gentamicin sulphate induced nephrotoxicity.

PMID: 18690652 [PubMed - indexed for MEDLINE]

Renal Protective

Neuroprotective

Toxicol In Vitro. 2008 Sep;22(6):1496-502. Epub 2008 May 20.

Neuroprotection by Spirulina platensis protean extract and phycocyanin against iron-induced toxicity in SH-SY5Y neuroblastoma cells.

Bermejo-Bescós P, **Piñero-Estrada E**, **Villar del Fresno AM**.

Departamento de Farmacología, Facultad de Farmacia, Universidad Complutense de Madrid, Avenida de la Complutense s/n, Madrid, Spain. bescos@farm.ucm.es

We investigated the effect of Spirulina platensis protean extract and the biliprotein phycocyanin isolated from this microalga, on the activities of the antioxidant enzymes SOD, CAT, GPx, and GR, lipid peroxidation inhibitory activity and glutathione levels after the iron induced oxidative stress in SH-SY5Y neuroblastoma cells. Iron is one of the most important agents that produce oxidative stress and decline of neuronal functions. S. platensis protean extract and phycocyanin exert the antioxidant activity by protecting the activity of the cellular antioxidant enzymes total GPx, GPx-Se and GR and by increasing reduced glutathione in cells against oxidative stress induced by iron. These results suggested that S. platensis protean extract is a powerful antioxidant through a mechanism related to antioxidant activity, capable of interfering with radical-mediated cell death. S. platensis may be useful in diseases known to be aggravated by reactive oxygen species and in the development of novel treatments for neurodegenerative disorders as long as iron has been implicated in the neuropathology of several neurodegenerative disorders such as Alzheimer's or Parkinson diseases.

PMID: 18572379 [PubMed - indexed for MEDLINE]

Exp Neurol. 2005 Dec;196(2):298-307. Epub 2005 Sep 19.

Blueberry- and spirulina-enriched diets enhance striatal dopamine recovery and induce a rapid, transient microglia activation after injury of the rat nigrostriatal dopamine system.

Strömberg I, Gemma C, Vila J, Bickford PC.

Department of Integrative Medical Biology, Umeå University, S 901 87 Umeå, Sweden. ingrid.stromberg@histocel.umu.se

Neuroinflammation plays a critical role in loss of dopamine neurons during brain injury and in neurodegenerative diseases. Diets enriched in foods with antioxidant and anti-inflammatory actions may modulate this neuroinflammation. The model of 6-hydroxydopamine (6-OHDA) injected into the dorsal striatum of normal rats, causes a progressive loss of dopamine neurons in the ventral mesencephalon. In this study, we have investigated the inflammatory response following 6-OHDA injected into the striatum of adult rats treated with diet enriched in blueberry or spirulina. One week after the dopamine lesion, a similar size of dopamine degeneration was found in the striatum and in the globus pallidus in all lesioned animals. At 1 week, a significant increase in OX-6- (MHC class II) positive microglia was found in animals fed with blueberry- and spirulina-enriched diets in both the striatum and the globus pallidus. These OX-6-positive cells were located within the area of tyrosine hydroxylase (TH) -negativity. At 1 month after the lesion, the number of OX-6-positive cells was reduced in diet-treated animals while a significant increase beyond that observed at 1 week was now present in lesioned control animals. Dopamine recovery as revealed by TH-immunohistochemistry was significantly enhanced at 4 weeks postlesion in the striatum while in the globus pallidus the density of TH-positive nerve fibers was not different from control-fed lesioned animals. In conclusion, enhanced striatal dopamine recovery appeared in animals treated with diet enriched in antioxidants and anti-inflammatory phytochemicals and coincided with an early, transient increase in OX-6-positive microglia.

Publication Types:

- Comparative Study
- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 16176814 [PubMed - indexed for MEDLINE]

Neuroprotective

Exp Neurol. 2005 May;193(1):75-84.

Dietary supplementation with blueberries, spinach, or spirulina reduces ischemic brain damage.

Wang Y, **Chang CF**, **Chou J**, **Chen HL**, **Deng X**, **Harvey BK**, **Cadet JL**, **Bickford PC**.

National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD 21224, USA.

Free radicals are involved in neurodegenerative disorders, such as ischemia and aging. We have previously demonstrated that treatment with diets enriched with blueberry, spinach, or spirulina have been shown to reduce neurodegenerative changes in aged animals. The purpose of this study was to determine if these diets have neuroprotective effects in focal ischemic brain. Adult male Sprague-Dawley rats were fed with equal amounts of diets (blueberry, spinach, and spirulina) or with control diet. After 4 weeks of feeding, all animals were anesthetized with chloral hydrate. The right middle cerebral artery was ligated with a 10-O suture for 60 min. The ligature was later removed to allow reperfusional injury. Animals were sacrificed and brains were removed for caspase-3 enzymatic assays and triphenyltetrazolium chloride staining at 8 and 48 h after the onset of reperfusion. A subgroup of animals was used for locomotor behavior and biochemical assays. We found that animals which received blueberry, spinach, or spirulina enriched diets had a significant reduction in the volume of infarction in the cerebral cortex and an increase in post-stroke locomotor activity. There was no difference in blood biochemistry, blood CO2, and electrolyte levels among all groups, suggesting that the protection was not indirectly mediated through the changes in physiological functions. Animals treated with blueberry, spinach, or spirulina had significantly lower caspase-3 activity in the ischemic hemisphere. In conclusion, our data suggest that chronic treatment with blueberry, spinach, or spirulina reduces ischemia/reperfusion-induced apoptosis and cerebral infarction.

Publication Types:

- Comparative Study
- Research Support, U.S. Gov't, Non-P.H.S.
- Research Support, U.S. Gov't, P.H.S.

PMID: 15817266 [PubMed - indexed for MEDLINE]

Neuroprotective

Diets enriched in foods with high antioxidant activity reverse age-induced decreases in cerebellar beta-adrenergic function and increases in proinflammatory cytokines.

- Gemma C,
- Mesches MH,
- Sepesi B,
- Choo K,
- Holmes DB,
- Bickford PC.

James A. Haley Veterans Affairs Medical Center, Tampa, Florida 33612, USA.

Antioxidants and diets supplemented with foods high in oxygen radical absorbance capacity (ORAC) reverse age-related decreases in cerebellar beta-adrenergic receptor function. We examined whether this effect was related to the antioxidant capacity of the food supplement and whether an antioxidant-rich diet reduced the levels of proinflammatory cytokines in the cerebellum. Aged male Fischer 344 rats were given apple (5 mg dry weight), spirulina (5 mg), or cucumber (5 mg) either in 0.5 ml water by oral gavage or supplied in the rat chow daily for 14 d. Electrophysiologic techniques revealed a significant decrease in beta-adrenergic receptor function in aged control rats. Spirulina reversed this effect. Apple (a food with intermediate ORAC) had an intermediate effect on cerebellar beta-adrenergic receptor physiology, and cucumber (low ORAC) had no effect, indicating that the reversal of beta-adrenergic receptor function decreases might be related to the ORAC dose. The mRNA of the proinflammatory cytokines tumor necrosis factor-alpha (TNFalpha) and TNFbeta was also examined. RNase protection assays revealed increased levels of these cytokines in the aged cerebellum. Spirulina and apple significantly downregulated this age-related increase in proinflammatory cytokines, whereas cucumber had no effect, suggesting that one mechanism by which these diets work is by modulation of an age-related increase in inflammatory responses. Malondialdehyde (MDA) was measured as a marker of oxidative damage. Apple and spirulina but not cucumber decreased MDA levels in the aged rats. In summary, the improved beta-adrenergic receptor function in aged rats induced by diets rich in antioxidants is related to the ORAC dose, and these diets reduce proinflammatory cytokine levels.

Nutr Neurosci. 2006 Oct-Dec;9(5-6):207-12.

Spirulina maxima pretreatment partially protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity.

Chamorro G, Pérez-Albiter M, Serrano-García N, Mares-Sámano JJ, Rojas P.

Laboratorio de Toxicología Preclínica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Apartado Postal 314, C.P, 11520 México, D.F., México.

Spirulina is an alga that has a high nutritional value and some of its biological activities are attributed to the presence of antioxidants. Oxidative stress is involved in Parkinson's disease. This study aims at evaluating the neuroprotective role of Spirulina maxima (Sp.) against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity, used as a model of Parkinson's disease. Ninety-six male C-57 black mice were pretreated with Spirulina for 14 days (25, 50, 100, 150 or 200 mg/kg, oral), followed by three MPTP administrations (30 mg/kg, intraperitoneal, i.p.). Animals were given Sp. for 8 additional days. After the treatment, the striatal dopamine (DA) content was analysed by high performance liquid chromatography, and lipid peroxidation was studied as an index of oxidative stress. Sp. pretreatment at 150 mg/kg partially prevented (51%) the DA-depleting effect of MPTP and blocked oxidative stress. Spirulina partially prevents MPTP neurotoxicity and oxidative stress, suggesting it could be a possible alternative in experimental therapy.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17263087 [PubMed - indexed for MEDLINE]

Neuroprotective

Heavy Metal Removal

Clin Toxicol (Phila). 2006;44(2):135-41.

Efficacy of spirulina extract plus zinc in patients of chronic arsenic poisoning: a randomized placebo-controlled study.

Misbahuddin M, Islam AZ, Khandker S, Ifthaker-Al-Mahmud, Islam N, Anjumanara.
Department of Pharmacology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. mmisbah@aitlbd.net

BACKGROUND: Millions of people in Bangladesh, India, Taiwan, and Chile are consuming high concentration of arsenic through drinking water, and thousands of them have already developed chronic arsenic poisoning. There is no specific treatment. Some authors suggest the use of vitamins and minerals for more than 6 months. The present placebo-controlled double-blind study was conducted to evaluate effectiveness of spirulina extract plus zinc in the treatment of chronic arsenic poisoning. METHODS: Forty-one patients of chronic arsenic poisoning were randomly treated orally by either placebo (17 patients) or spirulina extract (250 mg) plus zinc (2 mg) (24 patients) twice daily for 16 weeks. Each patient was supplied with arsenic-safe drinking water by installing a locally made water filter at household level. Effectiveness of spirulina extract plus zinc was evaluated by comparing changes in skin manifestations (clinical scores), arsenic contents in urine and hair, between the placebo- and spirulina extract plus zinc-treated groups. RESULTS: The concentrations of total arsenic in water (without filtration) of placebo- and spirulina extract plus zinc-treated groups were 150.1 +/- 18.3 and 161.7 +/- 23.9 microg/l, respectively. Intake of these high concentrations of arsenic lead to increased excretion of arsenic in urine (72.1 +/- 14.5 microg/l in placebo-treated group and 78.4 +/- 19.1 microg/l in spirulina plus zinc-treated group). After 2 weeks of using filtered water, there were significant reduction of both arsenic intake through water and urinary arsenic excretion (8.3 +/- 3.6 microg/l and 18.4 +/- 7.3 microg/l in placebo group; 9.7 +/- 5.4 microg/l and 21.6 +/- 5.8 microg/l) in spirulina extract plus zinc-treated group. There was a sharp increase in urinary excretion of arsenic (138 +/- 43.6 microg/l) at 4 weeks following spirulina plus zinc administration and the effect was continued for another 2 weeks. Spirulina extract plus zinc removed 47.1% arsenic from scalp hair. Spirulina extract had no major adverse effect that required physician's attention. The clinical scores (median) for melanosis before and after treatment with placebo was not statistically significant ($p > 0.05$), whereas in spirulina extract plus zinc-treated group it was statistically significant ($p < 0.01$). In cases of keratosis, the median clinical scores before and after treatment was not statistically significant ($p > 0.05$) in placebo-treated group. In spirulina extract plus zinc-treated group, the clinical scores for keratosis before and after treatment was statistically significant ($p < 0.05$). CONCLUSIONS: Results show that spirulina extract (250 mg) plus zinc (2 mg) twice daily for 16 weeks may be useful for the treatment of chronic arsenic poisoning with melanosis and keratosis.

Phytother Res. 2003 Apr;17(4):330-4.

Protective effect of Spirulina on lead induced deleterious changes in the lipid peroxidation and endogenous antioxidants in rats.

Upasani CD, **Balaraman R**.

Pharmacy Department, Faculty of Technology and Engineering, M S University of Baroda, Kalabhavan, Baroda-390 001, India.

The present study aims to investigate the protective effect of Spirulina on lead-induced changes in the levels of lipid peroxidation and endogenous antioxidants in liver, lung, heart, kidney and brain of rats. Levels of elemental lead were also measured in the organs of rats in all experimental groups. In the liver, lung, heart and kidney of lead-exposed animals, there was a significant ($p < 0.001$) increase in the lipid peroxidation and a decrease in the levels of endogenous antioxidants. Although, Spirulina did not affect the deposition of lead in organs apart from the brain, simultaneous administration of Spirulina to lead exposed animals significantly ($p < 0.001$) inhibited lipid peroxidation and restored the levels of endogenous antioxidants to normal. To conclude, Spirulina had a significant effect on scavenging free radicals, thereby protecting the organs from damage caused by the exposure to lead. Further more, Spirulina showed a significant ($p < 0.05$) decrease in the deposition of lead in the brain. Copyright 2003 John Wiley & Sons, Ltd.

PMID: 12722134 [PubMed - indexed for MEDLINE]

Mymensingh Med J. 2005 Jul;14(2):191-5.

Effect of hexane extract of spirulina in the removal of arsenic from isolated liver tissues of rat.

Saha SK, Misbahuddin M, Khatun R, Mamun IR.

Department of Pharmacology, MMC, Mymensingh.

The present study was conducted to investigate whether the active compound(s) of spirulina is present in its -- alcohol extract, hexane extract, DCM extract or in their residues. In phase I the accumulation of arsenic in isolated liver tissues of rat at different incubation period (15, 30, 45 minutes) was seen. In phase II arsenic-loaded liver tissues were incubated in presence and absence of alcohol extract, alcohol extraction residues, hexane extract, hexane extraction residues, DCM extract and DCM extraction residues of spirulina respectively. The percentage removal of arsenic from liver tissues by different extracts and residues of spirulina was estimated by Atomic Absorption Spectrophotometer. In phase III arsenic-loaded liver tissues were incubated in presence and absence of different concentration of hexane extract of spirulina and the percentage removal of arsenic from liver tissues was estimated. This study showed that the accumulation of arsenic in isolated liver tissue was time dependent and highest accumulation found was 0.69 microg/g tissues after 45 minutes incubation, which was highly significant. The percentage removal of arsenic from arsenic loaded liver tissues by alcohol extract, alcohol extraction residues, hexane extract, hexane extraction residues, DCM extract, DCM extraction residues were 33.8%,4.4%,83.0%,10.2%,7.3% and 2.9%, respectively. The percentage removal of arsenic by hexane extract at the concentration of 1, 10, 100 microg were 13.2%, 29.4% and 89.7%, respectively. Among the different extracts and residues of spirulina the hexane extract causes highly significant ($p<0.001$) removal. In conclusion the present study suggests that the active compound(s) of spirulina is present mostly in its hexane extract.

Publication Types:

- In Vitro

PMID: 16056210 [PubMed - indexed for MEDLINE]

Heavy Metal Removal

Indian J Exp Biol. 2005 Sep;43(9):773-81.

Effect of spirulina and Liv-52 on cadmium induced toxicity in albino rats.

Jeyaprakash K, **Chinnaswamy P**.

Department of Biochemistry, Dr NGPArts & Science College, Kovai Medical Center Research & Educational Trust, Coimbatore 641 014, India.
jeypee5@rediffmail.com

Oral administration of cadmium (6mg/kg body weight/day) as cadmium chloride (CdCl2) for 30 days resulted in a significant increase in thiobarbituric acid reactive substances (TBARS) level and a decrease in the levels of copper, zinc, iron, selenium, glutathione, superoxide dismutase, catalase, glutathione peroxidase when compared to normal control. Administration of either Liv-52 alone or in combination with spirulina produced a well pronounced protective effect in respect to these parameters in cadmium intoxicated rats. The protective effect of spirulina and Liv-52 in respect to biochemical changes were also confirmed by histopathological study in the liver and kidney sections.

PMID: 16187527 [PubMed - indexed for MEDLINE]

Ecotoxicol Environ Saf. 2008 May;70(1):121-6. Epub 2007 Jul 26.

Effect of extracts from Spirulina platensis bioaccumulating cadmium and zinc on L929 cells.

Pane L, Solisio C, Lodi A, Luigi Mariottini G, Converti A.

Dipartimento di Biologia, Università di Genova, Viale Benedetto XV, 5-I 16132 Genova, Italy.

The uptake of cadmium and zinc by Spirulina platensis was investigated using a laboratory culture of this cyanobacterium. The cells were treated with metal concentrations increasing from 0.5 to 2.0 mg L(-1), in order to evaluate their adsorption capacity and survival potential. Afterwards, the cytotoxicity of cell extracts bioaccumulating heavy metals was evaluated on cultured L929 mouse fibroblasts. Cadmium was removed with higher yield (84.0-88.7%) than zinc (54.5-68.0%) and the maximum specific removal of these metals was 1.82 and 2.60 mg g(-1), respectively. Cadmium bioaccumulating algal extracts caused higher cell mortality of L929 cells than zinc accumulating ones, with a clear dose-response trend. EC(50) estimated by Trimmed Spearman-Karber (TSK) method were 7.21 and 9.59cells mL(-1) for cadmium and zinc, respectively. The capability to accumulate heavy metals could have a remarkable importance for the utilization of algal species in human or animal feeding.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17662387 [PubMed - indexed for MEDLINE]

Phytother Res. 2007 Jan;21(1):44-6.

Effects of spirulina on the number of ovary mast cells in lead-induced toxicity in rats.

Karaca T, **Simşek N**.

University of Yüzüncü Yil, Faculty of Veterinary Medicine, Department of Histology and Embryology, Kampüs, 65080, Van, Turkey.
turankaraca74@hotmail.com

The present study investigated the protective effect of Spirulina against the lead-induced increase in mast cells in the ovary during the oestrous cycle of rats. In the ovary cortex and medulla of lead-exposed animals, there was a significant increase in the number of mast cells; however, when also treated with Spirulina, a decrease was observed. The number of mast cells when Spirulina (300 mg/kg) was used alone was not significantly different from that of the control group. These results indicate that Spirulina decreases the number of mast cells induced by lead in the cortex and medulla of rat ovary.

PMID: 17078112 [PubMed - indexed for MEDLINE]

J Hazard Mater. 2009 May 30;164(2-3):1304-9. Epub 2008 Sep 20.

Spirulina platensis feeding inhibited the anemia- and leucopenia-induced lead and cadmium in rats.

Simsek N, **Karadeniz A**, **Kalkan Y**, **Keles ON**, **Unal B**.

Department of Histology and Embryology,Faculty of Veterinary Medicine, University of Atatürk, Erzurum, Turkey.

In the present investigation, the effect of Spirulina platensis (Sp) was undertaken on rats fed with lead and cadmium including diet by using physiological, enzymehistochemical and stereological methods. For this aim, 50 rats were equally divided into five groups as control (C), lead (Pb), Spirulina+lead (Sp+Pb), cadmium (Cd), and Spirulina+cadmium (Sp+Cd). Red blood cell (RBC) and white blood cell (WBC) counts, packed cell volume (PCV), and haemoglobine (Hb) concentrations were determined by haemocytometric methods in blood samples collected on 30th day. Population of T lymphocyte was counted by the alpha-naphthyl acetate esterase (ANAE) staining method, and reticulocytes were counted by stereological method. The counts of RBC, WBC, and ANAE positive T lymphocyte, and the values of Hb, PCV, and MCHC were decreased in the Pb and Cd groups compared to control group. Also, the number of reticulocytes (polychromatofilic erythrocyte) increased in the Pb groups, whereas it decreased in the Cd group. On the other hand, these values were ceased by S. platensis in the treated groups. These results suggest that S. platensis supplementation may be useful in adjuvant treatment of leukemia and anemia caused by lead and cadmium toxication.

PMID: 18976856 [PubMed - indexed for MEDLINE]

Ecotoxicol Environ Saf. 2009 Jan;72(1):231-5. Epub 2008 Apr 18.

The effects of Panax ginseng and Spirulina platensis on hepatotoxicity induced by cadmium in rats.

Karadeniz A, **Cemek M**, **Simsek N**.

Department of Physiology, Faculty of Veterinary, University of Atatürk, Ilica, Erzurum, Turkey. karadenizali@gmail.com

Cadmium is an environmental and industrial cumulative pollutant that affects many organs, specially the liver. The protective effect of Spirulina platensis and Panax ginseng on cadmium-induced oxidative stress and hepatotoxicity was evaluated in adult female Wistar albino rats. At the end of the 1-month experimental period, all animals were fasted for 12h and liver samples were taken for the determination of malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD) and nitric oxide (NO) levels. S. platensis and P. ginseng treatments showed marked decrease lipid peroxidation and increase of the endogenous antioxidants levels. The cadmium-induced histopathological changes were also minimized with the tested extracts. These results suggest that S. platensis and P. ginseng might play a role in reducing the toxic effect of cadmium and its antioxidant properties seem to mediate such a protective effect.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18395256 [PubMed - indexed for MEDLINE]

Allergies

J Med Food. 2005 Spring;8(1):27-30.

Effects of a Spirulina-based dietary supplement on cytokine production from allergic rhinitis patients.

Mao TK, **Van de Water J**, **Gershwin ME**.

Division of Rheumatology/Allergy and Clinical Immunology, University of California at Davis, School of Medicine, Davis, California, USA.

Spirulina represents a blue-green alga that is widely produced and commercialized as a dietary supplement for modulating immune functions, as well as ameliorating a variety of diseases. We have previously shown that the in vitro culture of Spirulina with human peripheral blood mononuclear cells (PBMCs) modulated the production of cytokines. In the present study, we evaluated the impact of a Spirulina-based dietary supplement (Earthrise Nutritionals, Inc., Irvine, CA) on patients with allergic rhinitis by assessing the production of cytokines [interleukin (IL)-4, interferon (IFN)-gamma, and IL-2] critical in regulating immunoglobulin E-mediated allergy. In a randomized double-blinded crossover study versus placebo, allergic individuals were fed daily with either placebo or Spirulina, at 1,000 mg or 2,000 mg, for 12 weeks. PBMCs isolated before and after the Spirulina feeding were stimulated with phytohemagglutinin (PHA) prior to determining the levels of cytokine from cell culture supernatants. Although Spirulina seemed to be ineffective at modulating the secretion of Th1 cytokines (IFN-gamma and IL-2), we discovered that Spirulina, administered at 2,000 mg/day, significantly reduced IL-4 levels by 32% from PHA-stimulated cells. These results indicate that Spirulina can modulate the Th profile in patients with allergic rhinitis by suppressing the differentiation of Th2 cells mediated, in part, by inhibiting the production of IL-4. To our knowledge, this is the first human feeding study that demonstrates the protective effects of Spirulina towards allergic rhinitis.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 15857205 [PubMed - indexed for MEDLINE]

Eur Arch Otorhinolaryngol. 2008 Oct;265(10):1219-23. Epub 2008 Mar 15.

The effects of spirulina on allergic rhinitis.

Cingi C, **Conk-Dalay M**, **Cakli H**, **Bal C**.

Department of of ENT, Eskisehir Osmangazi University Medical Faculty, Eskisehir, Turkey. cemal@cemalcingi.com

The prevalence of allergic rhinitis is increasing globally due to various causes. It affects the quality life of a large group of people in all around the world. Allergic rhinitis still remains inadequately controlled with present medical means. The need of continuous medical therapy makes individuals anxious about the side effects of the drugs. So there is a need for an alternative strategy. Effects of spirulina, tinospora cordifolia and butterbur were investigated recently on allergic rhinitis in just very few investigations. Spirulina represents a blue-green alga that is produced and commercialized as a dietary supplement for modulating immune functions, as well as ameliorating a variety of diseases. This double blind, placebo controlled study, evaluated the effectiveness and tolerability of spirulina for treating patients with allergic rhinitis. Spirulina consumption significantly improved the symptoms and physical findings compared with placebo ($P < 0.001$***) including nasal discharge, sneezing, nasal congestion and itching. Spirulina is clinically effective on allergic rhinitis when compared with placebo. Further studies should be performed in order to clarify the mechanism of this effect.

Publication Types:

- Comparative Study
- Randomized Controlled Trial

PMID: 18343939 [PubMed - indexed for MEDLINE]

J Laryngol Otol. 2007 Aug;121(8):779-82. Epub 2006 Nov 24

'Complementary ENT': a systematic review of commonly used supplements.

Karkos PD, **Leong SC**, **Arya AK**, **Papouliakos SM**, **Apostolidou MT**, **Issing WJ**.

Department of Otolaryngology, University Hospital Aintree, Liverpool, UK.
pkarkos@aol.com

OBJECTIVE: To assess the evidence surrounding the use of certain complementary supplements in otolaryngology. We specifically focussed on four commonly used supplements: spirulina, Ginkgo biloba, Vertigoheel and nutritional supplements (cod liver oil, multivitamins and pineapple enzyme). MATERIALS AND METHODS: A systematic review of the English and foreign language literature. Inclusion criteria: in vivo human studies. Exclusion criteria: animal trials, in vitro studies and case reports. We also excluded other forms of 'alternative medicine' such as reflexology, acupuncture and other homeopathic remedies. RESULTS: Lack of common outcome measures prevented a formal meta-analysis. Three studies on the effects of spirulina in allergy, rhinitis and immunomodulation were found. One was a double-blind, placebo, randomised, controlled trial (RCT) of patients with allergic rhinitis, demonstrating positive effects in patients fed spirulina for 12 weeks. The other two studies, although non-randomised, also reported a positive role for spirulina in mucosal immunity. Regarding the use of Ginkgo biloba in tinnitus, a Cochrane review published in 2004 showed no evidence for this. The one double-blind, placebo-controlled trial that followed confirmed this finding. Regarding the use of Vertigoheel in vertigo, two double-blind RCTs and a meta-analysis were identified. The first RCT suggested that Vertigoheel was equally effective in reducing the severity, duration and frequency of vertigo compared with betahistine. The second RCT suggested that Vertigoheel was a suitable alternative to G. biloba in the treatment of atherosclerosis-related vertigo. A meta-analysis of only four clinical trials confirms that Vertigoheel was equally effective compared with betahistine, G. biloba and dimenhydrinate. Regarding multivitamins and sinusitis, two small paediatric pilot studies reported a positive response for chronic sinusitis and otitis media following a course of multivitamins and cod liver oil. Regarding bromelain (pineapple enzyme) and sinusitis, one randomised, multicentre trial including 116 children compared bromelain monotherapy to bromelain with standard therapy and standard therapy alone, for the treatment of acute sinusitis. The bromelain monotherapy group showed a faster recovery compared with the other groups. CONCLUSION: The positive effects of spirulina in allergic rhinitis and of Vertigoheel in vertigo are based on good levels of evidence, but larger trials are required. There is overwhelming evidence that G. biloba may play no role in tinnitus. There is limited evidence for the use of multivitamins in sinus symptoms, and larger randomised trials are required.

Publication Types:

PMID: 17125579 [PubMed - indexed for MEDLINE]

Allergies

Curr Opin Otolaryngol Head Neck Surg. 2009 Mar 2. [Epub ahead of print]

Complementary and alternative medicine for allergic rhinitis.

Man LX.

Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

PURPOSE OF REVIEW: Otolaryngologists and other physicians who diagnose and treat allergic rhinitis encounter patients who use complementary medicine and alternative remedies. This article reviews the recent literature regarding complementary and alternative therapies for the treatment of allergic rhinitis. RECENT FINDINGS: There are a myriad of modalities for treating allergic rhinitis. Few are studied with rigorous randomized, double-blind, placebo-controlled trials for clinical efficacy. Often, the biological mechanisms and adverse effects are even less well understood. A few therapies, including spirulina, butterbur, and phototherapy hold some promise. Thus far, complementary and alternative therapies have not been integrated into the general treatment armamentarium of allergic rhinitis. SUMMARY: Several studies report beneficial effects of certain alternative treatments for allergic rhinitis. Additional insight into the mechanisms of action, short-term and long-term effects, and adverse events is needed.

PMID: 19262383 [PubMed - as supplied by publisher]

J Nutr Sci Vitaminol (Tokyo). 1998 Dec;44(6):841-51.

Class specific influence of dietary Spirulina platensis on antibody production in mice.

Hayashi O, Hirahashi T, Katoh T, Miyajima H, Hirano T, Okuwaki Y.

Department of Health and Nutrition, Kagawa Nutrition University, Sakado, Japan.

In the present study, we investigated antibody productions of IgA and other classes, such as IgE and IgG1, in mice as possible evidence of the protective effects of Spirulina toward food allergy and microbial infection. An increase of IgE antibody level in the serum was observed in the mice that were orally immunized with crude shrimp extract as an antigen (Ag group). The antibody level, however, was not further enhanced by treatment with Spirulina extract (SpHW). IgG1 antibody, on the other hand, which was increased by antigen administration, was further enhanced by Spirulina extract. It was noted that the IgA antibody level in the intestinal contents was significantly enhanced by treatment with Spirulina extract concurrently ingested with shrimp antigen, in comparison with that of the Ag group treated with shrimp antigen alone. An enhancement of IgA antibody production by Spirulina extract was also observed in culture supernatant of lymphoid cells, especially in the spleen and mesenteric lymph node from mice treated with Spirulina extract for 4 weeks before antigen stimulation. These results suggest that Spirulina may at least neither induce nor enhance allergic reaction such as food allergy dependent on an IgE antibody, and that when ingested both concurrently with antigen and before antigen stimulation, it may significantly enhance the IgA antibody level to protect against allergic reaction.

PMID: 10197315 [PubMed - indexed for MEDLINE]

Biochem Pharmacol. 1998 Apr 1;55(7):1071-6.

Inhibitory effect of mast cell-mediated immediate-type allergic reactions in rats by spirulina.

Kim HM, **Lee EH**, **Cho HH**, **Moon YH**.

Department of Oriental Pharmacy, College of Pharmacy, Wonkwang University, Iksan, Chonbuk, South Korea. hmkim@med.wonkwang.ac.kr

We investigated the effect of spirulina on mast cell-mediated immediate-type allergic reactions. Spirulina dose-dependently inhibited the systemic allergic reaction induced by compound 48/80 in rats. Spirulina inhibited compound 48/80-induced allergic reaction 100% with doses of 100-1000 microg/g body weight, i.p. Spirulina (10-1000 microg/g body weight, i.p.) also significantly inhibited local allergic reaction activated by anti-dinitrophenyl (DNP) IgE. When rats were pretreated with spirulina at a concentration ranging from 0.01 to 1000 microg/g body weight, i.p., the serum histamine levels were reduced in a dose-dependent manner. Spirulina (0.001 to 10 microg/mL) dose-dependently inhibited histamine release from rat peritoneal mast cells (RPMC) activated by compound 48/80 or anti-DNP IgE. The level of cyclic AMP in RPMC, when spirulina (10 microg/mL) was added, transiently and significantly increased about 70-fold at 10 sec compared with that of control cells. Moreover, spirulina (10 microg/mL) had a significant inhibitory effect on anti-DNP IgE-induced tumor necrosis factor-alpha production. These results indicate that spirulina inhibits mast cell-mediated immediate-type allergic reactions in vivo and in vitro.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9605430 [PubMed - indexed for MEDLINE]

Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2005 Feb;30(1):96-8.

[Experimental study of spirulina platensis in treating allergic rhinitis in rats]

[Article in Chinese]

Chen LL, **Zhang SF**, **Huang DN**, **Tan JQ**, **He SH**.

Department of Otorhinolaryngology, Affiliated Hospital of Guangdong Medical College, Zhanjiang 524001, China.

OBJECTIVE: To determine the therapeutic effect of spirulina platensis in allergic rhinitis (AR). METHODS: Ovalbumin sensitized white rats used as AR animals were treated with spirulina platensis (SPP). At the end of the treatment, the differences in the behavior science were observed; the changes in the nasal mucosa and mast cell degranulation were studied pathologically; and the levels of serum histamine and total immunoglobulin (Ig) E were determined by enzyme-linked immune sorbent assay. RESULTS: The behavior science score of the SPP treatment group was lower than that of the negative control group ($P < 0.01$) ; inflammatory reaction of nasal mucosa in the SPP treatment group were remarkably relieved; the number of nasal mucosa mastocyte and mast cell degranulation in the SPP treatment group were lower than that of the negative control group ($P <0.01$). The levels of serum histamine and total IgE in the SPP treatment group were lower than that of the negative control group ($P <0.01$). It had no significant difference in the positive control group and the SPP treatment group and the blank control group ($P > 0.05$). CONCLUSION: Spirulina platensis can prevent and treat AR in rats, which implies the possibility of using spirulina platensis for AR patients in the future.

Publication Types:

- English Abstract
- Research Support, Non-U.S. Gov't

PMID: 15871200 [PubMed - indexed for MEDLINE]

Additional Areas of Research

Eur J Appl Physiol. 2006 Sep;98(2):220-6. Epub 2006 Aug 30.

Preventive effects of Spirulina platensis on skeletal muscle damage under exercise-induced oxidative stress.

Lu HK, **Hsieh CC**, **Hsu JJ**, **Yang YK**, **Chou HN**.

Sport Science Research Center, National Taiwan College of Physical Education, Taichung, Taiwan. hklu@ntcpe.edu.tw

The effects of spirulina supplementation on preventing skeletal muscle damage on untrained human beings were examined. Sixteen students volunteered to take Spirulina platensis in addition to their normal diet for 3-weeks. Blood samples were taken after finishing the Bruce incremental treadmill exercise before and after treatment. The results showed that plasma concentrations of malondialdehyde (MDA) were significantly decreased after supplementation with spirulina ($P < 0.05$). The activity of blood superoxide dismutase (SOD) was significantly raised after supplementation with spirulina or soy protein ($P < 0.05$). Both of the blood glutathione peroxidaes (GPx) and lactate dehydrogenase (LDH) levels were significantly different between spirulina and soy protein supplementation by an ANCOVA analysis ($P < 0.05$). In addition, the lactate (LA) concentration was higher and the time to exhaustion (TE) was significantly extended in the spirulina trail ($P < 0.05$). These results suggest that ingestion of S. platensis showed preventive effect of the skeletal muscle damage and that probably led to postponement of the time of exhaustion during the all-out exercise.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 16944194 [PubMed - indexed for MEDLINE]

Plant Foods Hum Nutr. 1993 Jan;43(1):29-35.

Effect of supplementation of blue green alga (Spirulina) on outcome of pregnancy in rats.

Kapoor R, **Mehta U**.

Department of Foods and Nutrition, Haryana Agricultural University, Hisar, India.

To study the supplementary effect of Spirulina, pregnant rats were fed 5 different kinds of diets (casein, Spirulina, wheat gluten, Spirulina + wheat gluten, Spirulina-without additional vitamins and minerals), each providing 22% protein during the period of pregnancy. The outcome of pregnancy was assessed from litter and dams' weight and litter size. Maternal weight gain was found to be maximum with Spirulina + wheat gluten and least with the wheat gluten diet. Rats receiving Spirulina containing diets produced significantly ($p < 0.05$) higher litter size than those receiving casein and wheat gluten. In spite of having higher litter size, Spirulina containing diet groups produced pups with birth weights comparable to those of casein. Spirulina appears to be a good dietary supplement during pregnancy.

PMID: 8464842 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Pregnancy

FEMS Immunol Med Microbiol. 2007 Jul;50(2):231-8. Epub 2007 May 22.

Antiadhesive property of microalgal polysaccharide extract on the binding of Helicobacter pylori to gastric mucin.

Loke MF, **Lui SY**, **Ng BL**, **Gong M**, **Ho B**.

Department of Microbiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

The emergence of antibiotic-resistant Helicobacter pylori is of concern in the treatment of H. pylori-associated gastroduodenal diseases. As the organism was reported to bind gastric mucin, we used porcine gastric mucin as substrate to assess the antiadhesive property of polysaccharides derived from Spirulina (PS), a commercially available microalga, against the binding of H. pylori to gastric mucin. Results show that polysaccharides prevented H. pylori from binding to gastric mucin optimally at pH 2.0, without affecting the viability of either bacteria or gastric epithelial cells, thus favouring its antiadhesive action in a gastric environment. Using ligand overlay analysis, polysaccharide was demonstrated to bind H. pylori alkyl hydroperoxide reductase (AhpC) and urease, which have shown here to possess mucin-binding activity. An in vivo study demonstrated that bacteria load was reduced by >90% in BALB/c mice treated with either Spirulina or polysaccharides. It is thus suggested that polysaccharides may function as a potential antiadhesive agent against H. pylori colonization of gastric mucin.

Publication Types:

- Research Support, Non-U.S. Gov't

Additional Areas of Research: H. Pylori (Gastric Ulcers)

Arch Latinoam Nutr. 1978 Jun;28(2):196-207.

[Nutritive value of the spirulina algae (Spirulina maxima)]

[Article in Spanish]

Tejada de Hernández I, **Shimada AS**.

Nine experiments were conducted, five of them in vivo to determine the limiting amino acids and digestibility of spiruline algae for the rat, and four in vitro to determine the digestibility of the product in pepsin and ruminal liquid. None of the amino acids studied (lysine, methionine, histidine) added alone or in combination to 10% protein (either crude or true) diets provided exclusively by spiruline, seems to be limiting although the results could be masked by the low palatability and acceptability of the product by the rats. The apparent digestibility of the algae was 67.4%. For the in vitro tests, the algae were subjected to several physical or chemical treatments, and the digestibility of the resulting product determined by four different techniques. In no case did the tested treatments have any effect on its digestibility.

Publication Types:

- English Abstract

PMID: 753178 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Protein Absorption

Indian J Physiol Pharmacol. 2005 Jan;49(1):57-64.

Effect of ambroxol, spirulina and vitamin-E in naphthalene induced cataract in female rats.

Haque SE, **Gilani KM**.

Department of Pharmacology, Faculty of Pharmacy, Jamia Hamdard, New Delhi - 110 062.

Anticataract activity of Ambroxol, Spirulina and Vitamin E was examined using the naphthalene cataract model. Adult female albino rats of Wistar strain weighing between 180 and 220 grams were taken and divided into eight groups. Group I received light liquid paraffin 5 ml/kg/ day p.o. for 6 weeks. Group II received naphthalene solution 0.5 gm/kg/ day p.o. for first three days and 1 gm/kg/day p.o. thereafter for six weeks. Group III received Ambroxol suspension in 0.5% carboxy methyl cellulose (CMC) at the dose of 100 mg/kg/day p.o. alongwith naphthalene. Group IV received Spirulina in distilled water at the dose of 1500 mg/kg/ day p.o. alongwith naphthalene. Group V received Vitamin E emulsion at the dose of 50 mg/kg/day p.o. alongwith naphthalene. Group VI received Ambroxol alone at the dose of 100 mg/kg/day p.o. Group VII received Spirulina alone at the dose of 1500 mg/kg/day p.o. Group VIII received vitamin E alone at the dose of 50 mg/kg/day p.o. Lens glutathione, soluble protein and water content profiles revealed the preventive role of Ambroxol, Spirulina and Vitamin E in naphthalene-induced cataract in female rats.

Publication Types:

- Comparative Study

PMID: 15881859 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Eye (Cataract)

Vopr Pitan. 2004;73(2):28-31.

[Essential trace elements distribution in food micro algae Spirulina platensis biomass fractions]

[Article in Russian]

Zaretskaia ES, **Gmoshinskiĭ IV**, **Mazo VK**, **Zorin SN**, **Aleshko-Ozhevskiĭ IuP**.

Distribution of some trace elements elements (zinc, selenium, iron, manganese, chromium) was characterized in enriched biomass of food micro algae Spirulina platensis by means of water-methanol fractionation. The majority of said trace elements was shown to be incorporated in intercellular hydrophylic fraction, e.g. could be connected to cellular proteins. This result enable the conclusion, that Spirulina is a suitable matrix for biotechnological incorporation of new food trace elements preparations.

Publication Types:

- English Abstract

PMID: 15154369 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Trace Minerals

Biotechnol J. 2007 Oct;2(10):1297-305.

New food sources of essential trace elements produced by biotechnology facilities.

Mazo VK, Gmoshinski IV, Zorin SN.

State Research Institute of Nutrition, Moscow, Russia.

Population satiety with trace elements (TE) is a problem that is widely discussed in nutrition science. For optimal nutrition, the form of TE eaten in food is very important. Organic forms of TE in nutrition are appropriate as human metabolism has adapted to these kinds of nutrients during species evolution. This is now considered a reason for the beneficial use of biotechnologically produced TE sources in human food. Advanced matrixes for TE incorporation are unicellular organisms such as yeast, lactobacilli and Spirulina. Addition of inorganic salts at certain concentrations into cultivation media enables the mineral ions to incorporate into the microbial biomass. As a consequence, the biomass becomes enriched with organic forms of incorporated TE, which are presented by their complexes with amino acids, proteins and probably lipids and polysaccharides. In addition, a new direction of research has made good advances, in which technology has been developed for production of organic forms of TE through complex formation between transition metals (zinc, copper, manganese, chromium, iron) with amino acids and peptides formed during enzymatic hydrolysis of food protein. This brief review discusses the results demonstrating the advances in the biotechnological production of new TE sources, to obtain food components destined for wide prophylaxis of TE deficiency or for dietary treatment of the adverse consequences of these deficiencies.

Publication Types:

- Review

PMID: 17546707 [PubMed - indexed for MEDLINE]

Nutr J. 2006 Jan 23;5:3.

Nutrition rehabilitation of undernourished children utilizing Spiruline and Misola.

Simpore J, **Kabore F**, **Zongo F**, **Dansou D**, **Bere A**, **Pignatelli S**, **Biondi DM**, **Ruberto G**, **Musumeci S**.

Unit of Formation and of Research in Sciences of Life and of the Earth, University of Ouagadougou, Burkina Faso, Africa. jacques.simpore@univ-ouaga.bf

BACKGROUND: Malnutrition constitutes a public health problem throughout the world and particularly in developing countries. AIMS : The objective of the study is to assess the impact of an elementary integrator composed of Spiruline (Spirulina platensis) and Misola (millet, soja, peanut) produced at the Centre Medical St Camille (CMSC) of Ouagadougou, Burkina Faso, on the nutritional status of undernourished children. MATERIALS AND METHODS: 550 undernourished children of less than 5 years old were enrolled in this study, 455 showed severe marasma, 57 marasma of medium severity and 38 kwashiorkor plus marasma. We divided the children randomly into four groups: 170 were given Misola (731 +/- 7 kcal/day), 170 were given Spiruline plus traditional meals (748 +/- 6 kcal/day), 170 were given Spiruline plus Misola (767 +/- 5 kcal/day). Forty children received only traditional meals (722 +/- 8 kcal/day) and functioned as the control group. The duration of this study was eight weeks. RESULTS AND DISCUSSION: Anthropometrics and haematological parameters allowed us to appreciate both the nutritional and biological evolution of these children. The rehabilitation with Spiruline plus Misola (this association gave an energy intake of 767 +/- 5 kcal/day with a protein assumption of 33.3 +/- 1.2 g a day), both greater than Misola or Spiruline alone, seems to correct weight loss more quickly. CONCLUSION: Our results indicate that Misola, Spiruline plus traditional meals or Spiruline plus Misola are all a good food supplement for undernourished children, but the rehabilitation by Spiruline plus Misola seems synergically favour the nutrition rehabilitation better than the simple addition of protein and energy intake.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 16430775 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Malnutrition

Rev Epidemiol Sante Publique. 2008 Dec;56(6):425-31. Epub 2008 Nov 17.

[The effect of spiruline during nutritional rehabilitation: systematic review]

[Article in French]

Halidou Doudou M, **Degbey H**, **Daouda H**, **Leveque A**, **Donnen P**, **Hennart P**, **Dramaix-Wilmet M**.

Pédiatrie A, hôpital National de Niamey, BP 238, Niamey, Niger.
mhalidou2002@yahoo.fr

BACKGROUND: To evaluate the impact of spiruline on nutritional rehabilitation. DATA SOURCES: Systematic search in medical and scientific databases (Medline, Cochrane, Embase) and other specific databases (PhD theses, reports...). METHODS: We selected studies in which spiruline was used as supplementation in malnourished patients, irrespective of the form and dose of spiruline and in controlled trials or not. Two persons made the selection separately. Nutritional status was estimated by anthropometric and biological measures. RESULTS: Thirty-one references were identified and seven studies were retained for this review; three randomized controlled and four non-controlled trials. Spiruline had a positive impact on weight in all studies. In non-controlled trials, the other parameters: arm circumference, height, albumin, prealbumin, protein and hemoglobin improved after spiruline supplementation. For these studies, methodology was the main drawback. None of the studies retained for analysis were double-blinded clinical trials and all involved small samples. Four of them did not have a control group for comparison. CONCLUSION: The impact of spiruline was positive for most of the considered variables. However, the studies taken into account in this review are of poor-methodological quality. A randomized, a large-sized double-blind controlled clinical trial with a longer follow-up should be conducted to improve current knowledge on the potential impact of spiruline on nutritional rehabilitation.

Publication Types:

- Comparative Study
- English Abstract
- Review

PMID: 19010626 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Malnutrition

Int J Neurosci. 2008 Nov;118(11):1523-33.

The effect of hydrolyzed Spirulina by malted barley on forced swimming test in ICR mice.

Kim NH, **Jeong HJ**, **Lee JY**, **Go H**, **Ko SG**, **Hong SH**, **Kim HM**, **Um JY**.

Department of Pharmacology, Institute of Oriental Medicine, Kyung Hee University, Seoul, Republic of Korea.

Spirulina is a true puree of a filamentous, spiral-shaped blue alga and exerts the useful properties as a source of many biochemicals. This study investigated the antidepressant-like effect of hydrolyzed Spirulina by malted barley on the forced swimming test in mice. After the forced swimming test, we examined the levels of several blood biochemical parameters in mice. The effect of the hydrolyzed Spirulina by malted barley-treated group for 2 weeks on the immobility time was significantly reduced in comparison with the control group ($p < .05$). Plasma level of blood urea nitrogen and lactate dehydrogenase was significantly decreased in the hydrolyzed Spirulina by malted barley-treated group compared with the control group ($p < .05$). It had no effect on the variation of creatine kinase, glucose, total protein, and albumin levels. Therefore, these results suggest that hydrolyzed Spirulina by malted barley might be a candidate among antidepressant agents.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18853331 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Anti-Depressant

Eur J Nutr. 2008 Oct;47(7):393-400. Epub 2008 Sep 18.

Spirulina enhanced the skeletal muscle protein in growing rats.

Voltarelli FA, **de Mello MA**.

Dept. of Physical Education, UNESP-São Paulo State University, 24-A Avenue, number 1515-District: Bela Vista, 13506-900, Rio Claro, SP, Brazil. faunesp8@yahoo.com.br

BACKGROUND/AIM OF THE STUDY: This study evaluates the effects of the blue green alga spirulina as the sole dietary source of protein on muscle protein in weaning rats. METHODS: Young (30 days) Wistar rats were fed, during 60 days, with 17% protein spirulina (S) and compared to rats fed 17% protein casein (C). We evaluated the muscle total protein and DNA contents and the in vitro protein synthesis and degradation rates as well the myosin protein expression. RESULTS: The groups presented similar body weight (C = 427.3 +/- 8.6; S = 434.6 +/- 7.7 g) and length (C = 25.4 +/- 0.2; S = 25.6 +/- 0.2 cm). Soleus muscle total protein (C = 2.9 +/- 0.1; S = 2.7 +/- 0.1 mg/100 mg) and DNA (C = 0.084 +/- 0.005; S = 0.074 +/- 0.005 mg/100 mg) contents were also similar in both groups. Protein degradation (C = 427.5 +/- 40.6; S = 476.7 +/- 50.5 pmol/mg(-1) h(-1)) did not differ between the groups but protein synthesis (C = 17.5 +/- 1.0; S = 25.2 +/- 1.9 pmol/mg(-1) h(-1)) and myosin content (western blot analyses) were higher ($P < 0.05$, t test) in spirulina group. CONCLUSIONS: Although the spirulina proved adequate protein quality to maintain body growth, the muscle protein synthesis rates were increased by the ingestion of the experimental diet in young rats.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18807105 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Muscle Protein Synthesis

Inflammopharmacology. 2009 Apr 24. [Epub ahead of print]

Evaluation of protective efficacy of Spirulina platensis against collagen-induced arthritis in rats.

Kumar N, **Singh S**, **Patro N**, **Patro I**.

School of Studies in Microbiology, Jiwaji University, Gwalior, 474011, Madhya Pradesh, India.

AIM: To assess the protective efficacy of Spirulina platensis against collagen-induced arthritis (CIA) in female Wistar rats based on the changes in paws thickness, serum albumin, cholesterol, lipid peroxidation, alkaline phosphatase and acid phosphatase activities and histology of paw joints. METHODS: Arthritis was induced by intradermal injection of Collagen and Freund's adjuvant incomplete suspension at several sites on the back with a dose of 2 mg kg(-1) of body weight and boosted with 0.1 ml intradermally at the base of the tail. CIA rats were orally treated with 200 and 400 mg kg(-1) per oral of S. platensis from 0 to 45th day. RESULTS: S. platensis at 400 mg kg(-1) per oral significantly elevates serum albumin and decreases the serum cholesterol, alkaline phosphatase and acid phosphatase activities, lipid peroxidation, paw thickness as well as normalize the joint histopathology of CIA rats. CONCLUSIONS: S. platensis (400 mg kg(-1)) significantly normalizes changes observed in arthritic rats to near normal conditions, indicates that S. platensis has promising protective efficacy against CIA rats.

PMID: 19390977 [PubMed - as supplied by publisher]

Additional Areas of Research: Arthritis

Guang Pu Xue Yu Guang Pu Fen Xi. 2001 Dec;21(6):868-70.

[Determination of micro-elements in natural spirulina using FAAS]

[Article in Chinese]

Duan M, **Ma WX**, **Li L**, **Sun XT**.

Loess Plateau Agricultural Testing Center, Shanxi Academy, Yangling 712100, China.

The analytic results show that the spirulina powder have a plenty of microelements(K, Na, Ca, Mg, Fe, Zn). Compared with that of rice, wheat flour, maize and soybean, the content of K, Na, Ca, Mg, Fe and Zn of it is respectively as from 4 to 10 times, from 10 to 80 times, from 25 to 70 times, from 3 to 15 times, from 4 to 36 times and from 4 to 24 times as theirs. The content of microelements of it compared with vegetable is much higher. The spirulina has a certain inhibition from cancer, high blood pressure, sugar diabetes and hasten body to absorb Se and Mo, and is of benefit to cardiac muscle. The experimental result indicated that spirulina was good health care food with value of nourish and medicinal.

Publication Types:

- English Abstract

PMID: 12958919 [PubMed - indexed for MEDLINE]

Additional Areas of Research: General Health

Curr Pharm Biotechnol. 2008 Oct;9(5):400-5.

Spirulina in health care management.

Kulshreshtha A, **Zacharia AJ**, **Jarouliya U**, **Bhadauriya P**, **Prasad GB**, **Bisen PS**.

School of Studies in Biochemistry and Biotechnology, Jiwaji University, Gwalior-474011, India.

Spirulina is a photosynthetic, filamentous, spiral-shaped and multicellular edible microbe. It is the nature's richest and most complete source of nutrition. Spirulina has a unique blend of nutrients that no single source can offer. The alga contains a wide spectrum of prophylactic and therapeutic nutrients that include B-complex vitamins, minerals, proteins, gamma-linolenic acid and the super anti-oxidants such as beta-carotene, vitamin E, trace elements and a number of unexplored bioactive compounds. Because of its apparent ability to stimulate whole human physiology, Spirulina exhibits therapeutic functions such as antioxidant, anti-bacterial, antiviral, anticancer, anti-inflammatory, anti-allergic and anti-diabetic and plethora of beneficial functions. Spirulina consumption appears to promote the growth of intestinal micro flora as well. The review discusses the potential of Spirulina in health care management.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 18855693 [PubMed - indexed for MEDLINE]

Introduction to Research on the Key Nutrients in Spirulina

Spirulina is the world's most nutrient rich SuperFood. Gram per gram, Spirulina has the highest concentration of nutrients and a greater variety of nutrients than any other food in the world. Here are just a few examples of how nutritious Spirulina is:

- Spirulina has 3100% more beta carotene than carrots
- Spirulina has 5100% more iron than spinach
- Spirulina has 180% more calcium than whole milk
- Spirulina has 670% more protein than tofu
- Three grams of Spirulina have more antioxidant and anti-inflammatory activity than five servings of vegetables
- Comparing phytonutrient levels, Spirulina is 31 times more potent than blueberries, 60 times more potent than spinach and 700 times more potent than apples

The variety of nutrients found in Spirulina is truly amazing. There are literally hundreds of different vitamins, minerals, carotenoids, amino acids, enzymes, essential fatty acids and phytonutrients found in quality Spirulina products. A thorough review of the benefits of all of these nutrients, or even most of these nutrients, is beyond the scope of this review. The editors instead chose to isolate several of the key nutrients abundantly found in Spirulina and look at the medical research that has been done on these nutrients.

The body of medical research on many of the nutrients reviewed is so vast that the editors felt it was necessary to conservatively limit the number of abstracts included in this reveiw. Published studies on nutrients like iron and beta carotene run into the thousands, and on all of the key nutrients reviewed published studies run into the hundreds. In the case of each section which follows, we have limited the abstracts included to a reasaonble number of studies performed since the year 2000. For further research, readers are requested to contact the editors at info@cyanotech.com or to search online themselves at www.pubmed.com

Beta carotene and Skin Health

Photochem Photobiol. 2008 Mar-Apr;84(2):284-8. Epub 2007 Dec 15.

Protection from sunburn with beta-Carotene--a meta-analysis.

Köpcke W, **Krutmann J**.

Department of Medical Informatics and Biomathematics, Münster University Hospital, Münster, Germany.

Nutritional protection against skin damage from sunlight is increasingly advocated to the general public, but its effectiveness is controversial. In this meta-analysis, we have systematically reviewed the existing literature on human supplementation studies on dietary protection against sunburn by beta-carotene. A review of literature until June 2007 was performed in PubMed, ISI Web of Science and EBM Cochrane library and identified a total of seven studies which evaluated the effectiveness of beta-carotene in protection against sunburn. Data were abstracted from these studies by means of a standardized data collection protocol. The subsequent meta-analysis showed that (1) beta-carotene supplementation protects against sunburn and (2) the study duration had a significant influence on the effected size. Regression plot analysis revealed that protection required a minimum of 10 weeks of supplementation with a mean increase of the protective effect of 0.5 standard deviations with every additional month of supplementation. Thus, dietary supplementation of humans with beta-carotene provides protection against sunburn in a time-dependent manner.

Publication Types:

- Meta-Analysis

PMID: 18086246 [PubMed - indexed for MEDLINE]

J Invest Dermatol. 2005 Feb;124(2):428-34.

beta-Carotene interferes with ultraviolet light A-induced gene expression by multiple pathways.

Wertz K, **Hunziker PB**, **Seifert N**, **Riss G**, **Neeb M**, **Steiner G**, **Hunziker W**, **Goralczyk R**.

DSM Nutritional Products, 205/217A, PO Box 3255, Department of Human Nutrition and Health, CH-4002 Basel, Switzerland. karin.wertz@dsm.com

Ultraviolet light A (UVA) exposure is thought to cause skin aging mainly by singlet oxygen ((1)O(2))-dependent pathways. Using microarrays, we assessed whether pre-treatment with the (1)O(2) quencher beta-carotene (betaC; 1.5 microM) prevents UVA-induced gene regulation in HaCaT human keratinocytes. Downregulation of growth factor signaling, moderate induction of proinflammatory genes, upregulation of immediate early genes including apoptotic regulators and suppression of cell cycle genes were hallmarks of the UVA effect. Of the 568 UVA-regulated genes, betaC reduced the UVA effect for 143, enhanced it for 180, and did not interact with UVA for 245 genes. The different interaction modes imply that betaC/UVA interaction involved multiple mechanisms. In unirradiated keratinocytes, gene regulations suggest that betaC reduced stress signals and extracellular matrix (ECM) degradation, and promoted keratinocyte differentiation. In irradiated cells, expression profiles indicate that betaC inhibited UVA-induced ECM degradation, and enhanced UVA induction of tanning-associated protease-activated receptor 2. Combination of betaC-promoted keratinocyte differentiation with the cellular "UV response" caused synergistic induction of cell cycle arrest and apoptosis. In conclusion, betaC at physiological concentrations interacted with UVA effects in keratinocytes by mechanisms that included, but were not restricted to (1)O(2) quenching. The retinoid effect of betaC was minor, indicating that the betaC effects reported here were predominantly mediated through vitamin A-independent pathways.

PMID: 15675964 [PubMed - indexed for MEDLINE]

Eur J Pharm Biopharm. 2009 May 12. [Epub ahead of print]

Cutaneous lycopene and beta-carotene levels measured by resonance Raman spectroscopy: High reliability and sensitivity to oral lactolycopene deprivation and supplementation.

Blume-Peytavi U, **Rolland A**, **Darvin ME**, **Pineau I**, **Voit C**, **Zappel K**, **Schäfer G**, **Meinke M**, **Sterry W**, **Lademann J**.

Clinical Research Center for Hair and Skin Science, Berlin, Germany.

Carotenoids, naturally occurring lipophilic micronutrients, possess an antioxidant activity associated with protection from damage induced by free radicals. The present study investigated an innovative non-invasive method to measure cutaneous levels of lycopene and beta-carotene and to monitor the distribution of orally administered lactolycopene in human skin and plasma. A double-blind placebo-controlled randomized study was performed in 25 volunteers, who were under a lycopene-deprived diet (4weeks prior to study until end of the study) and orally received either lactolycopene or placebo for 12weeks. Skin and plasma levels of lycopene and beta-carotene were monitored monthly using Raman spectroscopy and HPLC, respectively. Cutaneous levels of lycopene and beta-carotene monitored by resonance Raman spectroscopy showed high reliability. Irrespective of the investigated area, cutaneous levels were sensitive to lycopene deprivation and to oral supplementation; the forehead showed the closest correlation to lycopene variation in plasma. Plasma and skin levels of lycopene were both sensitive to oral intake of lactolycopene and, interestingly, also skin levels of beta-carotene. Thus, oral supplementation with lycopene led to an enrichment of beta-carotene in human skin, possibly due to the fact that carotenoids act in the skin as protection chains, with a natural protection against free radicals.

PMID: 19442725 [PubMed - as supplied by publisher]

Acta Dermatovenerol Alp Panonica Adriat. 2008 Dec;17(4):160-2, 164-6.

Beta-carotene in dermatology: Does it help?

Bayerl Ch.

Department of Dermatology and Allergology, HSK, Wilhelm Fresenius Klinik, Public Hospital, Teaching Hospital of the University of Mainz, Aukammallee 39, D-65191 Wiesbaden. christiane.bayerl@hsk-wiesbaden.de

UV irradiation of the skin leads to the induction of free radicals, carcinogenesis, and skin aging, and thus the use of beta-carotene in humans as a chaperoning agent is discussed. In the photohemolysis model, beta-carotene protects against the phototoxic effects of porphyrins. Beta-carotene should be used in erythropoietic protoporphyria, photosensitive diseases, and to reduce the effects of phototoxic drugs. Its effects on aging skin and on actinic keratosis have not yet been sufficiently studied.

Publication Types:

- Review

PMID: 19104740 [PubMed - indexed for MEDLINE]

Planta Med. 2008 Oct;74(13):1548-59. Epub 2008 Aug 11.

Phytochemicals as protectors against ultraviolet radiation: versatility of effects and mechanisms.

Dinkova-Kostova AT.

Biomedical Research Centre, Ninewells Hospital and Medical School, University of Dundee, Scotland, UK. a.dinkovakostova@dundee.ac.uk

Ultraviolet (UV) radiation is one of the most abundant carcinogens in our environment, and the development of non-melanoma skin cancers, the most common type of human malignancy worldwide, represents one of the major consequences of excessive exposure. Because of growing concerns that the level of UV radiation is increasing as a result of depletion of the stratospheric ozone and climate change, the development of strategies for protection of the skin is an urgent need. Many phytochemicals that belong to various families of secondary metabolites, such as alkaloids (caffeine, sanguinarine), flavonoids [(-)-epigallocatechin 3-gallate, genistein, silibinin], carotenoids (beta-carotene, lycopene), and isothiocyanates (sulforaphane), offer exciting platforms for the development of such protective strategies. These phytochemicals have been consumed by humans for many centuries as part of plant-rich diets and are presumed to be of low toxicity, an essential requirement for a chemoprotective agent. Mechanistically, they affect multiple signalling pathways and protect against UV radiation-inflicted damage by their ability to act as direct and indirect antioxidants, as well as anti-inflammatory and immunomodulatory agents. Such "pluripotent character" is a critical prerequisite for an agent that is designed to counteract the multiple damaging effects of UV radiation. Especially attractive are inducers of the Keap1/Nrf2/ARE pathway, which controls the gene expression of proteins whose activation leads to enhanced protection against oxidants and electrophiles. Such protection is comprehensive, long-lasting, and unlikely to cause pro-oxidant effects or interfere with the synthesis of vitamin D.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 18696411 [PubMed - indexed for MEDLINE]

J Nutr Biochem. 2009 May;20(5):389-98. Epub 2008 Jul 24.

Peroxidized cholesterol-induced matrix metalloproteinase-9 activation and its suppression by dietary beta-carotene in photoaging of hairless mouse skin.

Minami Y, **Kawabata K**, **Kubo Y**, **Arase S**, **Hirasaka K**, **Nikawa T**, **Bando N**, **Kawai Y**, **Terao J**.

Department of Food Science, Graduate School of Nutrition and Bioscience, University of Tokushima, Tokushima 770-8503, Japan.

The activation of matrix metalloproteinase (MMP)-9 leading to the formation of wrinkle and sagging of skin is an essential step in the skin photoaging on exposure to ultraviolet A (UVA). This study attempted to elucidate the role of peroxidized cholesterol including cholesterol hydroperoxides (Chol-OOHs), primary products of lipid peroxidation in biomembranes, in MMP-9 activation and the effect of dietary beta-carotene in MMP-9 activation. Hairless mice were subjected to periodic UVA irradiation for 8 weeks. The amount of peroxidized cholesterol detected as total hydroxycholesterol in the skin was increased significantly by the exposure. The activity and protein level of MMP-9 were elevated with wrinkling and sagging formation. MMP-9 activity was also enhanced by the intracutaneous injection of Chol-OOHs into the mouse skin. Adding beta-carotene to the diet of the mice during the period of irradiation suppressed the activity and expression of MMP-9 as well as the wrinkling and sagging formation. The amount of cholesterol 5alpha-hydroperoxide, a singlet molecular oxygen oxygenation-specific peroxidized cholesterol, was significantly lowered by the addition of beta-carotene to the diet. These results strongly suggest that Chol-OOHs formed on exposure to UVA contribute to the expression of MMP-9, resulting in photoaging. Dietary beta-carotene prevents the expression of MMP-9, at least partly, by inhibiting photodynamic action involved in the formation of Chol-OOHs.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18656335 [PubMed - in process]

Mol Biotechnol. 2007 Sep;37(1):26-30.

Carotenoids and flavonoids contribute to nutritional protection against skin damage from sunlight.

Stahl W, **Sies H**.

Institut für Biochemie und Molekularbiologie I, Heinrich-Heine-Universität Düsseldorf, Dusseldorf 40001, Germany.

The concept of photoprotection by dietary means is gaining momentum. Plant constituents such as carotenoids and flavonoids are involved in protection against excess light in plants and contribute to the prevention of UV damage in humans. As micronutrients, they are ingested with the diet and are distributed into light-exposed tissues, such as skin or the eye where they provide systemic photoprotection. beta-Carotene and lycopene prevent UV-induced erythema formation. Likewise, dietary flavanols exhibit photoprotection. After about 10-12 weeks of dietary intervention, a decrease in the sensitivity toward UV-induced erythema was observed in volunteers. Dietary micronutrients may contribute to life-long protection against harmful UV radiation.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 17914160 [PubMed - indexed for MEDLINE]

Skin Pharmacol Physiol. 2006;19(4):224-31. Epub 2006 May 4.

Antioxidant supplements improve parameters related to skin structure in humans.

Heinrich U, **Tronnier H**, **Stahl W**, **Béjot M**, **Maurette JM**.

Institute of Experimental Dermatology, University of Witten/Herdecke, Witten, Germany. ulrike.heinrich@uni-wh.de

In the present study we investigated the influence of two different antioxidant supplements composed of carotenoids, vitamin E and selenium on parameters related to skin health and skin aging. Thirty-nine volunteers with healthy, normal skin of skin type 2 were divided into 3 groups (n = 13) and supplemented for a period of 12 weeks. Group 1 received a mixture of lycopene (3 mg/day), lutein (3 mg/day), beta-carotene (4.8 mg/day), alpha-tocopherol (10 mg/day) and selenium (75 microg/day). Group 2 was supplemented with a mixture of lycopene (6 mg/day), beta-carotene (4.8 mg/day), alpha-tocopherol (10 mg/day) and selenium (75 microg/day). Group 3 was the placebo control. Upon supplementation serum levels of selected carotenoids increased in both verum groups. Skin density and thickness were determined by ultrasound measurements. A significant increase for both parameters was determined in the verum groups. Roughness, scaling, smoothness and wrinkling of the skin were determined by Surface Evaluation of Living Skin (Visioscan). Roughness and scaling were improved by the supplementation with antioxidant micronutrients. In the placebo group no changes were found for any of the parameters.

Publication Types:

- Controlled Clinical Trial

PMID: 16679825 [PubMed - indexed for MEDLINE]

Hautarzt. 2006 Apr;57(4):286, 288-90.

[Functional food and bioavailability in the target organ skin]

[Article in German]

Darwin M, **Schanzer S**, **Teichmann A**, **Blume-Peytavi U**, **Sterry W**, **Lademann J**.

Center of Experimental and Applied Cutaneous Physiology (CCP), Klinik für Dermatologie, Venerologie und Allergologie, Charité, Universitätsmedizin Berlin.

Reactive free radicals can be produced in the skin by the action of environmental factors, such as sun radiation and toxins. These radicals can damage the DNA, proteins and lipids of the living cells. The consequences can be skin aging, immune suppression and even skin cancer. Humans have developed a protective mechanism against the action of free radicals in the form of antioxidant substances. Several of these antioxidants cannot be produced by humans and have to be acquired via food, such as carotenoids. Optical, non-invasive methods, like resonance Raman spectroscopy, allow a qualitative and quantitative online detection of the kinetics of antioxidants such as carotenoids in the skin. By employing this method it has been shown that the uptake of carotenoids in food can lead to an accumulation in the skin. On the other hand, stress, illness and UV-radiation can reduce the concentration of antioxidant substances in the skin. A high concentration of antioxidant substances is protective and associated with a reduction in skin wrinkling.

Publication Types:

- English Abstract

PMID: 16485123 [PubMed - indexed for MEDLINE]

Hautarzt. 2006 Apr;57(4):281-5.

[Systemic photoprotection through carotenoids]

[Article in German]

Stahl W, **Krutmann J**.

Institut für Biochemie und Molekularbiologie I, Heinrich Heine-Universität Düsseldorf.

Nutritional supplements are increasingly used to protect human skin against environmentally-induced damage, most importantly as a consequence of ultraviolet radiation exposure. beta-carotene is a major constituent of comercially available products administered for systemic photoprotection. Studies on the systemic use of beta-carotene provide evidence that 15-30 mg/d over a period of about 10-12 wk produces a protective effect against UV-induced erythema. Similar effects have been attributed to mixtures of carotenoids or after long-term intake of dietary products rich in carotenoids. Supplementation with carotenoids contributes to basal protection of the skin but is not sufficent to obtain complete protection against severe UV irradiation.

Publication Types:

- English Abstract
- Review

PMID: 16463037 [PubMed - indexed for MEDLINE]

Int J Vitam Nutr Res. 2005 Jul;75(4):227-34.

Effects of administration of beta-carotene, ascorbic acid, persimmons, and pods on antioxidative ability in UV-irradiated ODS rats.

Hosotani K, **Yoshida M**, **Kitagawa M**.

Faculty of Education, Wakayama University, Japan. hosotani@center.wakayama-u.ac.jp

To evaluate the effects of supplementing diets with carotenoid and ascorbic acid (AsA) on the antioxidative ability of Osteogenic Disorder-Shionogi (ODS) rats, we added synthetic beta-carotene (betaC), AsA, and powders of persimmon (Ka) and pods (Po) containing betaC and AsA to the diet and obtained the following results. The urinary 8-hydroxydeoxyguanosine (8-OHdG) concentration was low in the -betaC.AsA and +AsA groups but high in the +betaC.AsA, +Ka, and +Po groups. The thiobarbituric acid-reactive substances (TBARS) in both the liver and skin were higher in the -betaC.AsA group than in the +betaC.AsA group and were low in the +Ka and +Po groups. As antioxidant enzymes, glutathione peroxidase (GSH-Px) activity was high in the +betaC.AsA group, low in the -beta3C.AsA group in both the skin and liver, and also high in the + Ka and +Po group in the liver. Superoxide dismutase (SOD) activity was high in the -betaC.AsA group and low in the +betaC.AsA and +Ka groups in both the skin and liver. Catalase (CAT) activity in the liver was low in the -betaC.AsA, +AsA, and +betaC groups and high in the +betaC.AsA and +Po groups. These results confirmed that the administration of betaC, AsA, and persimmons and pods increases antioxidative ability in the skin and liver of ultraviolet-b(UV-B)-irradiated ODS rats.

PMID: 16229338 [PubMed - indexed for MEDLINE]

Biochim Biophys Acta. 2005 May 30;1740(2):101-7. Epub 2004 Dec 28.

Bioactivity and protective effects of natural carotenoids.

Stahl W, **Sies H**.

Heinrich-Heine-University Duesseldorf, Institute of Biochemistry and Molecular Biology I, P.O. Box 101007, D-40001 Duesseldorf, Germany.
wilhelm.stahl@uni-duesseldorf.de

Carotenoids comprise a class of natural fat-soluble pigments which are found in numerous fruits and vegetables. The consumption of a diet rich in carotenoids has been epidemiologically correlated with a lower risk for several diseases. The antioxidant activity of carotenoids and biochemical properties influencing signaling pathways have been discussed as basic mechanisms of prevention. Conflicting data from intervention studies with beta-carotene to prevent cancers and cardiovascular disorders have challenged the concept. However, there is convincing evidence that carotenoids are important components of the antioxidant network. Photooxidative damage is suggested to be involved in the pathobiochemistry of several diseases affecting the skin and the eye, and carotenoids may protect light-exposed tissues. Lutein and zeaxanthin are the predominant carotenoids of the retina and are considered to act as photoprotectants preventing retinal degeneration. The unique distribution, localization and high levels of both carotenoids within the macula lutea as well as their physicochemical properties make them suitable candidates for photoprotection. beta-Carotene is used as an oral sun protectant for the prevention of sunburn and has been shown to be effective either alone or in combination with other carotenoids or antioxidant vitamins. Protective effects are also achieved with a diet rich in lycopene.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 15949675 [PubMed - indexed for MEDLINE]

Free Radic Biol Med. 2004 Dec 1;37(11):1854-63.

Participation of singlet oxygen in ultraviolet-a-induced lipid peroxidation in mouse skin and its inhibition by dietary beta-carotene: an ex vivo study.

Bando N, **Hayashi H**, **Wakamatsu S**, **Inakuma T**, **Miyoshi M**, **Nagao A**, **Yamauchi R**, **Terao J**.

Department of Food Science, Graduate School of Nutrition and Biosciences, The University of Tokushima, Tokushima 770-8503, Japan.

Dietary beta-carotene acts as a photoprotective agent in the skin, but the exact mechanism of protection is unknown. This ex vivo study is focused on determining the mechanism of action of beta-carotene against UV-A-induced skin damage by characterizing peroxidized phosphatidylcholine (PC) and beta-carotene oxidation products. BALB/c mice were fed with basal or a beta-carotene-supplemented diet, and homogenates from their dorsal skin were prepared after 3 weeks for UV-A irradiation. Analyses revealed that the degree of lipid peroxidation in the beta-carotene group was significantly lower than that in the controls. The isomeric composition of hydroperoxy fatty acids, constituting peroxidized PC, was determined by thin-layer chromatography-blotting followed by gas chromatography/mass spectrometry (MS)/selected ion monitoring analysis. The 9- and 10-isomers of peroxidized PC, resulting from the reaction of singlet molecular oxygen ((1)O(2)) with oleic acid, were elevated in the UV-A-exposed control group compared to the experimental group. Similar results were obtained from methylene-blue-sensitized photooxidation of mouse skin lipids in vitro. Liquid chromatography/MS analysis of the homogenates confirmed the formation of beta-carotene 5,8-endoperoxide, a specific marker for the (1)O(2) reaction. These results indicate that dietary beta-carotene accumulates in the skin and acts as a protective agent against UV-A-induced oxidative damage, by quenching the (1)O(2).

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15528044 [PubMed - indexed for MEDLINE]

Free Radic Biol Med. 2004 Sep 1;37(5):654-70.

Beta-carotene inhibits UVA-induced matrix metalloprotease 1 and 10 expression in keratinocytes by a singlet oxygen-dependent mechanism.

Wertz K, **Seifert N**, **Hunziker PB**, **Riss G**, **Wyss A**, **Lankin C**, **Goralczyk R**.

Department Human Nutrition and Health, Carotenoid Group, DSM Nutritional Products, Basel, Switzerland.

UVA exposure causes skin photoaging by singlet oxygen (1)O(2)-mediated induction of, e.g., matrix metalloproteases (MMPs). We assessed whether pretreatment with beta-carotene, a (1)O(2) quencher and retinoic acid (RA) precursor, interferes with UVA-induced gene regulation. HaCaT keratinocytes were precultured with beta-carotene at physiological concentrations (0.5, 1.5, and 3.0 microM) prior to exposure to UVA from a Hönle solar simulator (270 kJ/m(2)). HaCaT cells accumulated beta-carotene in a time- and dose-dependent manner. UVA irradiation massively reduced the cellular beta-carotene content. Beta-carotene suppressed UVA-induction of MMP-1, MMP-3, and MMP-10, three major matrix metalloproteases involved in photoaging. We show that regulation by not only MMP-1, but also MMP-10, involves (1)O(2)-dependent mechanisms. Beta-carotene dose-dependently quenched (1)O(2)-mediated induction of MMP-1 and MMP-10. Thus, as in chemical solvent systems, beta-carotene quenches (1)O(2) also in living cells. Vitamin E did not cooperate with beta-carotene to further inhibit MMP induction. HaCaT cells produced weak retinoid activity from beta-carotene, as demonstrated by mild upregulation of RAR beta and activation of an RARE-dependent reporter gene. Beta-carotene did not regulate the genes encoding other RARs, RXRs, or the two beta-carotene cleavage enzymes. These results demonstrate that beta-carotene acts photoprotectively, and that this effect is mediated by (1)O(2) quenching.

PMID: 15288123 [PubMed - indexed for MEDLINE]

Cancer Epidemiol Biomarkers Prev. 2004 Jun;13(6):1042-51.

Diet and melanoma in a case-control study.

Millen AE, **Tucker MA**, **Hartge P**, **Halpern A**, **Elder DE**, **Guerry D 4th**, **Holly EA**, **Sagebiel RW**, **Potischman N**.

Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-7344, USA. millena@mail.nih.gov

BACKGROUND: Malignant melanoma has been one of the most rapidly increasing cancers within the United States with few modifiable risk factors. This study investigates risk related to dietary factors, which are potentially modifiable. METHODS: Newly diagnosed patients with melanoma (n = 502) were recruited from pigment lesion clinics and controls (n = 565) were recruited from outpatient clinics. To investigate the relationship between melanoma and dietary factors in this case-control study, study subjects were requested to complete a food frequency questionnaire, which assessed diet over the previous year. Using logistic regression, odds ratios (ORs) for melanoma were computed for nutrient and alcohol intake. RESULTS: Persons in high versus low quintiles of energy-adjusted vitamin D, alpha-carotene, beta-carotene, cryptoxanthin, lutein, and lycopene had significantly reduced risk for melanoma (ORs < or = 0.67), which remained after adjustment for presence of dysplastic nevi, education, and skin response to repeated sun exposure. Addition of micronutrients from supplements did not add an additional reduction in risk. High alcohol consumption was associated with an increased risk for melanoma, which remained after adjustment for confounders [OR (95% confidence interval) in highest versus lowest quintiles, 1.65 (1.09-2.49)]. CONCLUSIONS: Diets consisting of foods rich in vitamin D and carotenoids and low in alcohol may be associated with a reduction in risk for melanoma. These analyses should be repeated in large, prospective studies.

PMID: 15184262 [PubMed - indexed for MEDLINE]

Photochem Photobiol Sci. 2003 Jun;2(6):655-9.

Betacarotene supplementation protects from photoaging-associated mitochondrial DNA mutation.

Eicker J, **Kürten V**, **Wild S**, **Riss G**, **Goralczyk R**, **Krutmann J**, **Berneburg M**.

Institut für Umweltmedizinische Forschung gGmbH at the Heinrich-Heine-University, Auf' m Hennekamp 40, D-40225 Düsseldorf, Germany.

Mutations of mitochondrial DNA accumulate during normal aging and can be detected at elevated levels in skin prematurely aged by chronic exposure to ultraviolet (UV) light (photoaging). In normal human fibroblasts, we have previously demonstrated that mtDNA deletions are induced by repetitive exposure to sublethal doses of UVA radiation mediated through singlet oxygen. Betacarotene is a known quencher of ROS and singlet oxygen in particular, and it is widely applied in photoprotective compounds. Therefore we investigated whether in our in vitro system, betacarotene is capable of protecting from the induction of photoaging-associated mtDNA deletions. All-E (trans) betacarotene was tested at doses from 0.25 to 3.0 microM for uptake into cells as well as its protective capacity. Assessment of cellular uptake of all-E betacarotene measured by HPLC revealed a dose dependent increase of intracellular concentrations, as well as an increase in oxidative metabolites. UVA-exposure led to a decrease of all-E-betacarotene, its Z-isomers and oxidative metabolites. Assessment of mtDNA deletions by PCR revealed reduced levels of mtDNA mutagenesis in cells coincubated with betacarotene at concentrations of 0.5 microM and higher. Taken together, these results indicate that betacarotene (i) is taken up into the cell in a dose dependent manner, (ii) interacts with UVA radiation in the cell and (iii) shows protective properties from the induction of a photoaging-associated mtDNA mutation.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 12859149 [PubMed - indexed for MEDLINE]

Free Radic Biol Med. 2003 Feb 15;34(4):456-64.

Beta-carotene suppresses UVA-induced HO-1 gene expression in cultured FEK4.

Trekli MC, **Riss G**, **Goralczyk R**, **Tyrrell RM**.

Department of Pharmacy and Pharmacology, University of Bath, Bath, United Kingdom.

The ultraviolet region of sunlight causes a significant oxidative stress to human skin cells and modulates expression of a series of genes in dermal fibroblasts and other cell types. The human heme oxygenase 1 (HO-1) gene is strongly activated within the first hours that follow UVA irradiation of normal human dermal fibroblasts (FEK4) and this response is being used as a marker of oxidative stress in cells. It has been shown that the induction of this gene occurs via singlet oxygen ((1)O(2)) produced upon interaction of UVA radiation with an as yet undefined cellular chromophore. Carotenoids, as the most potent singlet oxygen quenchers in nature, are expected to effectively suppress the UVA-induced HO-1 gene activation in human cells. In this study, we measured the suppression of UVA-induced levels of HO-1 mRNA after the addition of a series of six all-trans-beta-carotene concentrations (0.07, 0.2, 0.8, 2.3, 8.0, and 21 microM) to the culture medium of exponentially growing FEK4 cells. The corresponding levels of beta-carotene uptake and apo-carotenal formation were measured following HPLC separation. The results of this study show a concentration-dependent suppression of UVA- (250 kJ/m(2)) induced transcriptional activation of HO-1 in exponentially growing FEK4 cells by beta-carotene. Suppression occurred at concentrations that have been observed in human plasma after dietary supplementation with beta-carotene.

PMID: 12566071 [PubMed - indexed for MEDLINE]

J Nutr. 2003 Jan;133(1):98-101.

Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema.

Heinrich U, **Gärtner C**, **Wiebusch M**, **Eichler O**, **Sies H**, **Tronnier H**, **Stahl W**.

Institut für Experimentelle Dermatologie, Universität Witten-Herdecke, Germany.

Carotenoids are useful oral sun protectants, and supplementation with high doses of beta-carotene protects against UV-induced erythema formation. We compared the erythema-protective effect of beta-carotene (24 mg/d from an algal source) to that of 24 mg/d of a carotenoid mix consisting of the three main dietary carotenoids, beta-carotene, lutein and lycopene (8 mg/d each). In a placebo-controlled, parallel study design, volunteers with skin type II (n = 12 in each group) received beta-carotene, the carotenoid mix or placebo for 12 wk. Carotenoid levels in serum and skin (palm of the hand), as well as erythema intensity before and 24 h after irradiation with a solar light simulator were measured at baseline and after 6 and 12 wk of treatment. Serum beta-carotene concentration increased three- to fourfold ($P < 0.001$) in the beta-carotene group, whereas in the mixed carotenoid group, the serum concentration of each of the three carotenoids increased one- to threefold ($P < 0.001$). No changes occurred in the control group. The intake of either beta-carotene or a mixture of carotenoids similarly increased total carotenoids in skin from wk 0 to wk 12. No changes in total carotenoids in skin occurred in the control group. The intensity of erythema 24 h after irradiation was diminished in both groups that received carotenoids and was significantly lower than baseline after 12 wk of supplementation. Long-term supplementation for 12 wk with 24 mg/d of a carotenoid mix supplying similar amounts of beta-carotene, lutein and lycopene ameliorates UV-induced erythema in humans; the effect is comparable to daily treatment with 24 mg of beta-carotene alone.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 12514275 [PubMed - indexed for MEDLINE]

Carcinogenesis. 2002 Aug;23(8):1263-5.

The effect of beta-carotene on lung and skin carcinogenesis.

Wolf G.

Department of Nutritional Sciences and Toxicology, University of California, Berkeley CA 94720-3104, USA. retinol@nature.berkeley.edu

The induction of pre-cancerous squamous metaplasia in lungs of ferrets by high doses of dietary beta-carotene (BC) and cigarette smoke is compared with and contrasted to the different effects of high doses of dietary BC on skin papilloma and carcinoma induction by the two-stage carcinogenesis protocol. Whereas high dietary BC can inhibit the conversion of skin papillomas to carcinomas, such treatment would not be expected to inhibit smoke-induced lung tumors.

Publication Types:

- Comparative Study

PMID: 12151342 [PubMed - indexed for MEDLINE]

FEBS Lett. 2001 Dec 7;509(2):186-90.

The effect of beta-carotene on the expression of interleukin-6 and heme oxygenase-1 in UV-irradiated human skin fibroblasts in vitro.

Obermüller-Jevic UC, **Schlegel B**, **Flaccus A**, **Biesalski HK**.

Department of Biological Chemistry and Nutrition, University of Hohenheim, Fruwirthstrasse 12, 70593, Stuttgart, Germany. biesal@uni-hohen.heim.de

beta-Carotene is discussed as an anti-oxidant micronutrient and singlet oxygen quencher in human skin, protecting against UV light-induced damage. However, we recently demonstrated that beta-carotene has a pro-oxidant potential in cultured human skin fibroblasts because it enhances the UVA induction of heme oxygenase-1 (HO-1). Herein, we further show that beta-carotene also strongly promotes the UVA induction of pro-inflammatory interleukin-6 (IL-6) in skin fibroblasts in vitro. Singlet oxygen quencher sodium azide abrogated up-regulation of IL-6, and likewise also of HO-1. In UVB-irradiated cells, beta-carotene did not modulate levels of IL-6 and HO-1. The observed effects might be relevant for UV-induced inflammatory processes.

PMID: 11741586 [PubMed - indexed for MEDLINE]

Beta carotene and Immunity

Biosci Biotechnol Biochem. 2008 Jun;72(6):1595-600. Epub 2008 Jun 7.

Ingested beta-carotene enhances glutathione level and up-regulates the activity of cysteine cathepsin in murine splenocytes.

Takeda S, **Bando N**, **Yamanishi R**.

Department of Food Science, Graduate School of Nutrition and Biosciences, The University of Tokushima, Japan.

To elucidate health benefits of beta-carotene, especially on immunity, we measured redox-related indices in spleen cells from BALB/c mice supplemented with various amounts of beta-carotene. In mice supplemented with beta-carotene in their diet, glutathione, an intracellular anti-oxidation agent, increased in their splenocytes. This change was highly correlated with the accumulation of beta-carotene, but not with that of retinol. The increase in glutathione was accompanied by an increase in mRNA for gamma-glutamylcysteine synthetase, a rate-limiting enzyme for glutathione synthesis. The higher the glutathione content was in the spleen cells, the higher the activity of cysteine cathepsin became in crude antigen-presenting cells contained in the spleen. These data suggest that accumulated beta-carotene in splenocytes, without being metabolized, caused an increase in the intracellular glutathione level, thereby anti-oxidatively supporting the activity of redox-sensitive lysosomal protease, which is involved in antigen-presentation.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18540097 [PubMed - indexed for MEDLINE]

Physiol Behav. 2009 Mar 2;96(3):389-93. Epub 2008 Nov 12.

Maternal effects and beta-carotene assimilation in Canary chicks.

Tanvez A, **Amy M**, **Chastel O**, **Leboucher G**.

Laboratoire d'Ethologie et Cognition Comparées, Université Paris X-Nanterre, BSL, 200 avenue de république, 92001 Nanterre, France.
aurelietanvez@gmail.com

Carotenoids are pigments responsible for the red, orange and yellow coloration of plants and animals. They may be beneficial in two ways; they have a powerful antioxidant activity, and they can behave as an immunostimulant. Animals however cannot synthesize carotenoids de novo, they must obtain them through their diet. In our experiments on Canaries, we investigated how mothers transfer their dietary carotenoid-related benefits to their offspring; either through the egg, or through the diet (during chicks' feeding). Female Canaries were allowed to access beta-carotene enriched food during egg formation and/or chicks' feeding. We sorted the chicks into four groups using the period when they assimilated the beta-carotene as a variable. The four groups were: (i) before hatching (from yolk), (ii) after hatching (from maternal feeding), (iii) before and after hatching, or (iv) never. Colorimetry and HPLC analysis from sub-samples of yolks confirmed the maternal transfer of dietary carotenoids to the yolk. Our results show that benefits from maternal dietary carotenoids are transferred to the chicks, but according to the period when they are assimilated by the chicks, the physiological effects are different. It was found that the chicks' growth was enhanced when carotenoids were assimilated both before and after hatching. However an increase in cellular immunity efficiency only occurs when the assimilation takes place after hatching.

Publication Types:

- Comparative Study

PMID: 19059274 [PubMed - indexed for MEDLINE]

Vet J. 2008 Apr;176(1):70-6. Epub 2008 Mar 5.

Role of antioxidants and trace elements in health and immunity of transition dairy cows.

Spears JW, **Weiss WP**.

Department of Animal Science and Interdepartmental Nutrition Program, North Carolina State University, Raleigh, NC 27695-7621, USA.
Jerry_Spears@ncsu.edu

A number of antioxidants and trace minerals have important roles in immune function and may affect health in transition dairy cows. Vitamin E and beta-carotene are important cellular antioxidants. Selenium (Se) is involved in the antioxidant system via its role in the enzyme glutathione peroxidase. Inadequate dietary vitamin E or Se decreases neutrophil function during the perpariturient period. Supplementation of vitamin E and/or Se has reduced the incidence of mastitis and retained placenta, and reduced duration of clinical symptoms of mastitis in some experiments. Research has indicated that beta-carotene supplementation may enhance immunity and reduce the incidence of retained placenta and metritis in dairy cows. Marginal copper deficiency resulted in reduced neutrophil killing and decreased interferon production by mononuclear cells. Copper supplementation of a diet marginal in copper reduced the peak clinical response during experimental Escherichia coli mastitis. Limited research indicated that chromium supplementation during the transition period may increase immunity and reduce the incidence of retained placenta.

Publication Types:

- Review

PMID: 18325801 [PubMed - indexed for MEDLINE]

Gen Comp Endocrinol. 2008 Apr 1;156(2):418-25. Epub 2008 Jan 18.

Yolk testosterone levels and dietary carotenoids influence growth and immunity of grey partridge chicks.

Cucco M, **Guasco B**, **Malacarne G**, **Ottonelli R**, **Tanvez A**.

University of Piemonte Orientale, DISAV Dipartimento di Scienze dell'Ambiente e della Vita, via Bellini 25, Alessandria, Italy. marco.cucco@unipmn.it

Early maternal effects in the form of substances accumulated in the egg, such as carotenoids and hormones, can be physiologically relevant for a good development of offspring. It has been found in different species that testosterone (T) can be beneficial to offspring by increasing growth rate, but detrimental by reducing immunocompetence and increasing oxidative stress. Carotenoids on the other hand are suggested to be beneficial because they can counteract the oxidative stress and the immune-depressive effect of T. In this study we analyzed the effect of prenatal T exposure in the grey partridge. We injected eggs with three doses of T (high, intermediate, and physiological). After hatching, chicks exposed to a prenatal high dose of T were fed with two diets (rich or poor) differing in beta-carotene content. We found a significant effect of T on both chick growth and cell-mediated immunity, with high T doses resulting in detrimental effects while low doses were beneficial. Detrimental effects of the high dose of T on immunity were mitigated by beta-carotene consumed in the diet. The differences between groups were observed in the early period of life (age 10 days for mass, and age 10 and 21 days for immunity), and disappeared in the following period, and up to 1 and 2 years later. Overall, our observations show that T in the egg is not detrimental but beneficial, and that negative effects are found only at supraphysiological concentrations. The negative effects of T on immunity could be balanced if chicks could consume a diet rich in beta-carotene.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18299130 [PubMed - indexed for MEDLINE]

Comp Biochem Physiol A Mol Integr Physiol. 2007 Aug;147(4):1038-46. Epub 2007 Mar 19.

Effects of beta-carotene on adult immune condition and antibacterial activity in the eggs of the Grey Partridge, Perdix perdix.

Cucco M, **Guasco B**, **Malacarne G**, **Ottonelli R**.

University of Piemonte Orientale, DiSAV, via Bellini 25, I-15100 Alessandria, Italy. cucco@unipmn.it

Carotenoids are important dietary constituents in birds. Their functions are numerous and complex, and breeding females are potentially faced with an optimal allocation of these resources between themselves and offspring. We conducted a dietary experiment (low and high supply of beta-carotene) to examine the effect of beta-carotene on health and immune response of 64 reproducing pairs of Grey Partridge (Perdix perdix L.) and on the quality of their eggs, as revealed by the measurement of biochemical components in yolk and albumen, the egg hatching rate and chick survival. We found a beneficial effect of beta-carotene on the erythrosedimentation rate and immune response of females (PHA reaction), while the diet did not significantly affect these variables in males. In both sexes, the plasma level of carotenoids was not related to the quantity of beta-carotene supplied. A higher quantity of beta-carotene in the diet did not induce a variation of egg nutrients (proteins and lipids), nor an increase of yolk beta-carotene concentration. We detected a higher concentration of lysozyme, an enzyme with antibacterial activity, in the albumen of eggs laid by females with a high supply of beta-carotene. These eggs showed higher hatching rates. The present study indicates that although carotenoid supplementation does not influence blood and yolk carotenoid levels, it results in better immune conditions of females, eventually translated into increased antibacterial activity of the eggs. The broad range of beneficial effects of carotenoids is discussed.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17462926 [PubMed - indexed for MEDLINE]

J Nutr. 2006 Oct;136(10):2606-10.

Immunity and antioxidant capacity in humans is enhanced by consumption of a dried, encapsulated fruit and vegetable juice concentrate.

Nantz MP, **Rowe CA**, **Nieves C Jr**, **Percival SS**.

Food Science and Human Nutrition Department University of Florida Gainesville, Florida 32611, USA.

The daily consumption of fruits and vegetables is a common dietary recommendation to support good health. We hypothesized that a commercially available encapsulated fruit and vegetable juice powder concentrate (FVJC) could support functional indices of health due to increased intake of various phytonutrients. This was a double-blind, randomized, placebo-controlled investigation of 59 healthy law students who consumed either FVJC or placebo capsules for 77 d. Blood was collected on d 1, 35, and 77 to examine the number of circulating alphabeta- and gammadelta-T cells, cytokine production, lymphocyte DNA damage, antioxidant status, and levels of carotenoids and vitamin C. A log of illnesses and symptoms was also kept. The FVJC group tended to have fewer total symptoms than the placebo group ($P < 0.076$). By d 77 there was a 30% increase in circulating gammadelta-T cells and a 40% reduction in DNA damage in lymphocytes in the FVJC group relative to the placebo group. Plasma levels of vitamin C and of beta-carotene, lycopene, and lutein increased significantly from baseline in the FVJC group as did plasma oxygen radical absorptive capacity (50%). Interferon-gamma produced by phorbol-stimulated lymphocytes was reduced 70% in the FVJC group, whereas other cytokines (IL-4, IL-6, transforming growth factor beta) were unchanged relative to treatment or time. FVJC consumption during this study period resulted in increased plasma nutrients and antioxidant capacity, reduction in DNA strand breaks, and an increase in circulating gammadelta-T cells.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 16988134 [PubMed - indexed for MEDLINE]

Behav Processes. 2006 Nov 1;73(3):325-32. Epub 2006 Aug 12.

Effects of beta-carotene supplementation on chick growth, immune status and behaviour in the grey partridge, Perdix perdix.

Cucco M, **Guasco B**, **Malacarne G**, **Ottonelli R**.

University of Piemonte Orientale, Department of Environmental and Life Sciences, DiSAV, via Bellini 25, I-15100 Alessandria, Italy. cucco@unipmn.it <cucco@unipmn.it>

Carotenoids are important for various functions during chick development. Since these pigments cannot be synthesized, they can be considered limited resources that the mother optimally allocates between herself and her offspring (maternal effect). Some studies have examined the effects of carotenoids on growth and immune function but little is known about their role in behaviour. In this study of the grey partridge, we conducted two supplementation experiments: (1) laying females were fed with beta-carotene enriched or impoverished diets; (2) chicks were fed directly with beta-carotene enriched or impoverished diets. We then evaluated the effects of this carotenoid on chick growth, immunocompetence and anti-predator behaviour (reactions to a raptor model). In the first experiment, the beta-carotene enriched diet given to mothers did not cause any difference in chick physiology. In the second experiment, beta-carotene supplementation of chicks had a significant beneficial effect on their growth and immune response, although their behavioural reactions did not differ in relation to the diet. Therefore, beta-carotene supplementation had beneficial effects on growth and immunocompetence only when directly supplied to chicks. The beneficial effect reported in other species for begging or pecking behaviours was not confirmed for the anti-predator behaviour of grey partridge chicks.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 16963199 [PubMed - indexed for MEDLINE]

Clin Exp Allergy. 2006 Aug;36(8):993-1000.

Associations between antioxidant status, markers of oxidative stress and immune responses in allergic adults.

Dunstan JA, **Breckler L**, **Hale J**, **Lehmann H**, **Franklin P**, **Lyons G**, **Ching SY**, **Mori TA**, **Barden A**, **Prescott SL**.

School of Paediatrics and Child Health, University of Western Australia, Perth, WA, Australia.

BACKGROUND: There has been growing interest in the role of antioxidant function in controlling inflammatory disease states, such as allergy. This study investigated the relationship between antioxidant status, markers of airways inflammation [exhaled nitric oxide (eNO)], oxidative stress (F(2) isoprostanes) and immune responses in allergic adults. METHODS: Antioxidants (vitamins C, E, beta-carotene and selenium) and total antioxidant capacity (tAC) in serum were examined in relation to eNO, plasma F(2) isoprostanes and peripheral blood mononuclear cell (PBMC) cytokine and lymphoproliferative response to house dust mite (HDM) allergen, Staphylococcus enterotoxin B (SEB), phytohaemaglutinin (PHA) and lipopolysaccharide (LPS) in 54 allergic adults. RESULTS: Firstly, levels of specific vitamins did not correlate with tAC. Secondly, we did not see any evidence that specific vitamin levels (or tAC) were associated with either polarization or attenuation of in vitro immune responses. If anything, there were positive correlations between antioxidant (vitamin C and selenium) levels and HDM allergen responses [lymphoproliferation (selenium; r=0.35, P=0.013) and both Th2 IL13 (vitamin C; tau=0.254, P=0.028) and Th1 IFN-gamma (vitamin C; tau=0.302, P=0.009) responses]. There were also significant positive relationships between antioxidant levels and IL-10 responses to polyclonal stimulation by SEB (r=0.292, P=0.036) and LPS (r=0.34, P=0.015) (beta-carotene) and PHA (r=0.34, P=0.021) (tAC). Thirdly, although airways inflammation (eNO) was associated with both in vitro and in vivo (skin test reactivity) to HDM, we did not see any correlation between eNO and oxidative stress (F(2)-isoprostanes). Finally, there were no consistent relationships between oxidative stress and immune responses. CONCLUSION: There was no evidence that higher antioxidant levels were associated with reduced allergen responsiveness in allergic adults. If anything, antioxidant status was associated with increased immune responsiveness. The significance of this needs to be addressed in future intervention studies.

Publication Types: Research Support, Non-U.S. Gov't

Pancreas. 2004 Aug;29(2):e45-50.

Natural beta-carotene for the prevention of post-ERCP pancreatitis.

Lavy A, **Karban A**, **Suissa A**, **Yassin K**, **Hermesh I**, **Ben-Amotz A**.

Gastroenterology Unit, Bnai-Zion Medical Center, Haifa, Israel.
lavya@netvision.net.il

OBJECTIVE: Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly used procedure. Pancreatitis is its most common complication. As the injury may be mediated by oxidative stress, it could be ameliorated by antioxidants. METHODS: We conducted a double-blind trial, giving the patients a single dose of natural beta-carotene or placebo, 12 hours prior to procedure, and monitoring them for 24 hours post-procedure for procedure complications, antioxidant levels, and plasma oxidation. RESULTS: The overall incidence of acute pancreatitis according to our definition was 9.6%. The incidence of pancreatitis was not significantly different between the beta-carotene group (10%) and the placebo group (9.4%). Four patients in the placebo group had severe pancreatitis (2.22%), but none in the beta-carotene group. This difference is statistically significant. CONCLUSION: We did not see a reduction in the incidence of post-ERCP pancreatitis, but there may be some protective effect of treatment with beta-carotene regarding the severity of disease.

Publication Types:

- Clinical Trial
- Comparative Study
- Randomized Controlled Trial

PMID: 15257114 [PubMed - indexed for MEDLINE]

Fish Shellfish Immunol. 2004 Apr;16(4):527-37.

Enhancement of innate immunity in rainbow trout (Oncorhynchus mykiss Walbaum) associated with dietary intake of carotenoids from natural products.

Amar EC, **Kiron V**, **Satoh S**, **Watanabe T**.

Tokyo University of Marine Science and Technology, Minato, Japan.

The effects of orally administered carotenoids from natural sources on the non-specific defense mechanisms of rainbow trout were evaluated in a nine-week feeding trial. Fish were fed four diets containing either beta-carotene or astaxanthin at 100 and 200 mg kg-1 from the marine algae Dunaliella salina and red yeast Phaffia rhodozyma, respectively, and a control diet containing no supplemented carotenoids. Specific growth rate and feed:gain ratio were not affected by dietary carotenoid supplementation. Among the humoral factors, serum alternative complement activity increased significantly in all carotenoid supplemented groups when compared to the control. On the other hand, serum lysozyme activity increased in the Dunaliella group but not in the Phaffia group, whereas plasma total immunoglobulin levels were not altered by the feeding treatments. As for the cellular responses, the superoxide anion production from the head kidney remained unchanged while the phagocytic rate and index in all supplemented groups were significantly higher than those of the control. These findings demonstrate that dietary carotenoids from both D. salina and P. rhodozyma can modulate some of the innate defense mechanisms in rainbow trout.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 15123294 [PubMed - indexed for MEDLINE]

J Nutr. 2004 Jan;134(1):257S-261S.

Carotenoid action on the immune response.

Chew BP, **Park JS**.

Department of Animal Sciences, Washington State University, Pullman, WA 99164-6351, USA. boonchew@wsu.edu

Early studies demonstrating the ability of dietary carotenes to prevent infections have left open the possibility that the action of these carotenoids may be through their prior conversion to vitamin A. Subsequent studies to demonstrate the specific action of dietary carotenoids have used carotenoids without provitamin A activity such as lutein, canthaxanthin, lycopene and astaxanthin. In fact, these nonprovitamin A carotenoids were as active, and at times more active, than beta-carotene in enhancing cell-mediated and humoral immune response in animals and humans. Another approach to study the possible specific role of dietary carotenoids has used animals that are inefficient converters of carotenoids to vitamin A, for example the domestic cat. Results have similarly shown immuno-enhancement by nonprovitamin A carotenoids, based either on the relative activity or on the type of immune response affected compared to beta-carotene. Certain carotenoids, acting as antioxidants, can potentially reduce the toxic effects of reactive oxygen species (ROS). These ROS, and therefore carotenoids, have been implicated in the etiology of diseases such as cancer, cardiovascular and neurodegenerative diseases and aging. Recent studies on the role of carotenoids in gene regulation, apoptosis and angiogenesis have advanced our knowledge on the possible mechanism by which carotenoids regulate immune function and cancer.

Publication Types:

- Review

PMID: 14704330 [PubMed - indexed for MEDLINE]

J Vet Intern Med. 2003 Nov-Dec;17(6):835-42.

Effects of age and dietary beta-carotene on immunological variables in dogs.

Massimino S, **Kearns RJ**, **Loos KM**, **Burr J**, **Park JS**, **Chew B**, **Adams S**, **Hayek MG**.

Research and Development, The Iams Company, Lewisburg, OH, USA.

beta-Carotene is a naturally occurring carotenoid reported to have health-promoting effects in several species. Advancing age is known to have a negative impact on various immune variables in several species. This study was conducted in order to assess the effect of age on immune response in dogs and to determine whether beta-carotene is able to reverse this age-associated decline. To test this hypothesis, young and old dogs (n = 36) were fed either a control diet or experimental diets containing supplemental beta-carotene for 2-month periods. Age significantly (P < .05) lowered CD4+ T cell populations (47.2% versus 33.7%; young-control versus old-control, respectively) and beta-carotene restored percent distributions in old dogs to nonsignificance versus younger controls (41.0%). T cell proliferation was lower in old dogs (30,254 +/- 2,248 versus 14,811 +/- 2,497 cCPM; young-control versus old-control, respectively; P < .05), and beta-carotene supplementation significantly improved responses in this age group (21,329 +/- 2,275 cCPM). Although B cell proliferation was depressed with age (17,967 +/- 1,384 versus 7,535 +/- 1,469 cCPM; young-control versus old-control, respectively; P < .05), beta-carotene supplementation improved B cell proliferation in young dogs (23,500 +/- 1,339 cCPM). Old dogs displayed lower delayed-type hypersensitivity test (DTH) responses versus younger controls to both phytohemagglutinin-P (PHA; 11.1 +/- 0.95 versus 7.57 +/- 1.15 mm; young-control versus old-control, respectively; P < .05) and sheep red blood cell (RBC; 9.12 +/- 0.62 versus 8.08 +/- 0.75 mm; young-control versus old-control, respectively; P < .10). beta-Carotene improved these responses, mostly within the first 24-48 hours after injection. In summary, older dogs have lower immunological responses compared with younger controls. beta-Carotene supplementation significantly restored immune responses in older dogs when compared with their age-matched controls and younger counterparts.

PMID: 14658721 [PubMed - indexed for MEDLINE]

J Infect Dis. 2000 Sep;182 Suppl 1:S5-10.

Micronutrients and innate immunity.

Erickson KL, **Medina EA**, **Hubbard NE**.

Department of Cell Biology and Human Anatomy, University of California, School of Medicine, Davis, CA 95616-8643, USA. klerickson@ucdavis.edu

Micronutrients such as zinc, selenium, iron, copper, beta-carotene, vitamins A, C, and E, and folic acid can influence several components of innate immunity. Select micronutrients play an important role in alteration of oxidant-mediated tissue injury, and phagocytic cells produce reactive oxidants as part of the defense against infectious agents. Thus, adequate micronutrients are required to prevent damage of cells participating in innate immunity. Deficiencies in zinc and vitamins A and D may reduce natural killer cell function, whereas supplemental zinc or vitamin C may enhance their activity. The specific effects of micronutrients on neutrophil functions are not clear. Select micronutrients may play a role in innate immunity associated with some disease processes. Future studies should focus on issues such as age-related micronutrient status and innate immunity, alterations of micronutrients in disease states and their effect on innate immunity, and the mechanisms by which micronutrients alter innate immunity.

Publication Types:

- Review

PMID: 10944478 [PubMed - indexed for MEDLINE]

J Nutr. 2000 Aug;130(8):1910-3.

Dietary beta-carotene stimulates cell-mediated and humoral immune response in dogs.

Chew BP, **Park JS**, **Wong TS**, **Kim HW**, **Weng BB**, **Byrne KM**, **Hayek MG**, **Reinhart GA**.

Department of Animal Sciences, Washington State University, Pullman, WA 99164-6351, USA.

The role of beta-carotene on immune response in domestic dogs is not known. Female Beagle dogs were fed 0, 2, 20 or 50 mg beta-carotene/d; blood was sampled at wk 0, 1, 2, 4 and 8 for analysis of the following: lymphoproliferation, leukocyte subpopulations and concentrations of interleukin-2 (IL-2), immunoglobulin (Ig)G and IgM. Delayed-type hypersensitivity (DTH) response was assessed at wk 0, 3 and 7. beta-Carotene supplementation increased plasma beta-carotene concentrations in a dose-dependent manner. Compared with unsupplemented dogs, those fed 20 or 50 mg of beta-carotene had higher CD4+ cell numbers and CD4:CD8 ratio. However, there was no treatment difference in CD8+, CD21+ and major histocompatability complex (MHC) class II+ cells. Plasma IgG, but not IgM concentration was higher in dogs fed beta-carotene throughout the study period. The DTH response to phytohemagglutinin (PHA) and vaccine was heightened in beta-carotene-supplemented dogs. beta-Carotene feeding did not influence mitogen-induced lymphocyte proliferation or IL-2 production. Immune response was impaired in dogs classified as low beta-carotene absorbers compared with similar dogs fed the same amount of beta-carotene. Therefore, dietary beta-carotene heightened cell-mediated and humoral immune responses in dogs.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 10917901 [PubMed - indexed for MEDLINE]

Clin Infect Dis. 1998 Mar;26(3):711-8.

The significance of vitamin A and carotenoid status in persons infected by the human immunodeficiency virus.

Nimmagadda A, **O'Brien WA**, **Goetz MB**.

Department of Medicine, Veterans Affairs Medical Center, West Los Angeles, California 90073, USA.

Hyporetinemia is associated with increased childhood morbidity and mortality that is reversible with vitamin A supplementation. Although vitamin A deficiency is otherwise rare in developed countries, the prevalence of hyporetinemia in human immunodeficiency virus (HIV)-infected persons is up to 29%. Hyporetinemic HIV-infected patients have a 3.5-5-fold increased risk of death. Furthermore, HIV-infected patients with very low or very high intake of vitamin A and beta-carotene (a vitamin A precursor) have greater rates of disease progression than do patients with intermediate intake. In developing countries up to 60% of HIV-infected pregnant women are hyporetinemic. In such women the relative risk of perinatal HIV transmission may be increased more than fourfold. These data indicate that vitamin A deficiency is common in HIV-infected patients in the developed world and strongly suggest that vitamin A supplementation may be especially useful in adjunctive therapy for HIV-infected pregnant women who reside in the developing world.

Publication Types:

- Review

PMID: 9524850 [PubMed - indexed for MEDLINE]

Beta Carotene as a Chemopreventative

Carcinogenesis. 2008 Nov;29(11):2153-61. Epub 2008 Jul 16.

The sensitivity to beta-carotene growth-inhibitory and proapoptotic effects is regulated by caveolin-1 expression in human colon and prostate cancer cells.

Palozza P, **Sestito R**, **Picci N**, **Lanza P**, **Monego G**, **Ranelletti FO**.

Institute of General Pathology, Catholic University School of Medicine, Largo F. Vito 1, Rome 00168, Italy. p.palozza@rm.unicatt.it

Although several mechanisms have been proposed to explain the putative role of beta-carotene in cancer, no studies have investigated a possible influence of beta-carotene on caveolin-1 (cav-1) pathway, an important intracellular signaling deregulated in cancer. Here, different human colon and prostate cancer cell lines, expressing (HCT-116, PC-3 cells) or not (Caco-2, LNCaP cells) cav-1, were treated with varying concentrations of beta-carotene (0.5-30 muM) for different periods of time (3-72 h) and the effects on cell growth were investigated. The results of this study show that (i) beta-carotene acted as a growth-inhibitory agent in cav-1-positive cells, but not in cav-1-negative cells; (ii) in cav-1-positive cells, the carotenoid downregulated in a dose- and time-dependent manner the expression of cav-1 protein and messenger RNA levels and inhibited AKT phosphorylation which, in turn, stimulated apoptosis by increasing the expression of beta-catenin and c-myc and the activity of caspases-3, -7, -8 and -9; when the carotenoid was removed from culture medium, a progressive increase in cell growth was observed with respect to beta-carotene-treated cells and (iii) the transfection of cav-1 in cav-1-negative cells increased cell sensitivity to beta-carotene by inducing apoptosis. This effect was accompanied by a reduction of both cav-1 and AKT phosphorylation and by an increase of c-myc and beta-catenin expression. Silencing of c-Myc attenuated beta-carotene-induced apoptosis and beta-catenin expression. All together, these data suggest that the modulation of cav-1 pathway by beta-carotene could be a novel mechanism by which the carotenoid acts as a potent growth-inhibitory agent in cancer cells.

PMID: 18635524 [PubMed - indexed for MEDLINE]

J Natl Cancer Inst. 2006 Feb 15;98(4):245-54.

Comment in:

- J Natl Cancer Inst. 2006 Feb 15;98(4):225-7.

Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk.

Kirsh VA, **Hayes RB**, **Mayne ST**, **Chatterjee N**, **Subar AF**, **Dixon LB**, **Albanes D**, **Andriole GL**, **Urban DA**, **Peters U**; **PLCO Trial**.

Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD 20892, USA.

BACKGROUND: We evaluated the association between intake of these micronutrient antioxidants from foods and supplements and the risk of prostate cancer among men in the screening arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. At baseline, trial participants completed a 137-item food frequency questionnaire that included detailed questions on 12 individual supplements. Cox proportional hazards models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs). All statistical tests were two-sided. RESULTS: We identified 1338 cases of prostate cancer among 29 361 men during up to 8 years of follow-up. Overall, there was no association between prostate cancer risk and dietary or supplemental intake of vitamin E, beta-carotene, or vitamin C. However, among current and recent (i.e., within the previous 10 years) smokers, decreasing risks of advanced prostate cancer (i.e., Gleason score > or = 7 or stage III or IV) were associated with increasing dose (RR for > 400 IU/day versus none = 0.29, 95% CI = 0.12 to 0.68; Ptrend = .01) and duration (RR for > or = 10 years of use versus none = 0.30, 95% CI = 0.09 to 0.96; Ptrend = .01) of supplemental vitamin E use. Supplemental beta-carotene intake at a dose level of at least 2000 microg/day was associated with decreased prostate cancer risk in men with low (below the median of 4129 microg/day) dietary beta-carotene intake (RR = 0.52, 95% CI = 0.33 to 0.81). Among smokers, the age-adjusted rate of advanced prostate cancer was 492 per 100,000 person-years in those who did not take supplemental vitamin E, 153 per 100,000 person-years in those who took more than 400 IU/day of supplemental vitamin E, and 157 per 100,000 person-years in those who took supplemental vitamin E for 10 or more years. Among men with low dietary beta-carotene intake, the age-adjusted rate of prostate cancer was 1122 per 100,000 person-years in those who did not take supplemental beta-carotene, and 623 per 100,000 person-years in those who took at least 2000 microg/day of supplemental beta-carotene. CONCLUSIONS: Our results do not provide strong support for population-wide implementation of high-dose antioxidant supplementation for the prevention of prostate cancer. However, vitamin E supplementation in male smokers and beta-carotene supplementation in men with low dietary beta-carotene intakes were associated with reduced risk of this disease.

Publication Types:

- Multicenter Study
- Research Support, N.I.H., Extramural

Braz J Med Biol Res. 2006 Feb;39(2):203-10. Epub 2006 Feb 2.

Lycopene and beta-carotene protect in vivo iron-induced oxidative stress damage in rat prostate.

Matos HR, **Marques SA**, **Gomes OF**, **Silva AA**, **Heimann JC**, **Di Mascio P**, **Medeiros MH**.

Departamento de Fisiologia, Universidade Federal de Sergipe, São Cristóvão, SE, Brazil.

It has been suggested that iron overload may be carcinogenic. In the present study, we evaluated the effect of plasma and prostate carotenoid concentration on oxidative DNA damage in 12-week-old Wistar rats treated with intraperitoneal (ip) ferric nitrilotriacetate (Fe-NTA) (10 mg Fe/kg). Plasma beta-carotene and lycopene concentrations were measured as a function of time after ip injection of carotenoids (10 mg kg(-1) day(-1) beta-carotene or lycopene) in rats. The highest total plasma concentration was reached 3 and 6 h after ip injection of lycopene or beta-carotene, respectively. After 5 days of carotenoid treatment, lycopene and beta-carotene were present in the 0.10-0.51 nmol/g wet tissue range in the prostate. Using a sensitive method to detected 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodGuo) by HPLC/EC, the level of 8-oxodGuo in rat prostate DNA was significantly higher (6.3 +/- 0.6 residues/10(6) dGuo) 3 h after Fe-NTA injection compared with control rats (1.7 +/- 0.3 residues/10(6) dGuo). Rats supplemented with lycopene or beta-carotene for 5 days prior to Fe-NTA treatment showed a reduction of about 70% in 8-oxodGuo levels to almost control levels. Compared with control rats, the prostate of Fe-NTA-treated animals showed a 78% increase in malondialdehyde accumulation. Lycopene or beta-carotene pre-treatment almost completely prevented lipid damage. Epidemiological studies have suggested a lower risk of prostate cancer in men reporting a higher consumption of tomato products. However, before associating this effect with tomato sauce constituents, more information is required. The results described here may contribute to the understanding of the protective effects of carotenoids against iron-induced oxidative stress.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16470307 [PubMed - indexed for MEDLINE]

Carcinogenesis. 2006 Jul;27(7):1410-9. Epub 2006 Jan 9.

Combined antioxidant (beta-carotene, alpha-tocopherol and ascorbic acid) supplementation increases the levels of lung retinoic acid and inhibits the activation of mitogen-activated protein kinase in the ferret lung cancer model.

Kim Y, **Chongviriyaphan N**, **Liu C**, **Russell RM**, **Wang XD**.

Nutrition and Cancer Biology Laboratory, Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111, USA.

Interactions among beta-carotene (BC), alpha-tocopherol (AT) and ascorbic acid (AA) led to the hypothesis that using a combination of these antioxidants could be more beneficial than using a single antioxidant alone, particularly against smoke-related lung cancer. In this investigation, we have conducted an animal study to determine whether combined BC, AT and AA supplementation (AOX) protects against 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung carcinogenesis in smoke-exposed (SM) ferrets. Ferrets were treated for 6 months in the following four groups: (i) control, (ii) SM + NNK, (iii) AOX and (iv) SM + NNK + AOX. Results showed that the combined AOX supplementation (i) prevented the SM + NNK-decreased lung concentrations of retinoic acid (RA) and BC; (ii) inhibited the SM + NNK-induced phosphorylation of Jun N-terminal kinase (JNK), extracellular-signal-regulated protein kinase (ERK) and proliferating cellular nuclear antigen proteins in the lungs of ferrets; and (iii) blocked the SM + NNK-induced up-regulation of total p53 and Bax proteins, as well as phosphorylated p53 in the lungs of ferrets. In addition, there were no lesions observed in the lung tissue of ferrets in the control and/or the AOX groups after 6 months of intervention, but combined AOX supplementation resulted in a trend toward lower incidence of both preneoplastic lung lesions and lung tumor formation in SM + NNK + AOX group of ferrets, as compared with the SM + NNK group alone. These data indicate that combined AOX supplementation could be a useful chemopreventive strategy against lung carcinogenesis through maintaining normal tissue levels of RA and inhibiting the activation of mitogen-activated protein kinase pathways, cell proliferation and phosphorylation of p53.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 16401635 [PubMed - indexed for MEDLINE]

Beta Carotene as a Chemopreventative

Am J Clin Nutr. 2006 Jan;83(1):163-9.

Modification of lymphocyte DNA damage by carotenoid supplementation in postmenopausal women.

Zhao X, **Aldini G**, **Johnson EJ**, **Rasmussen H**, **Kraemer K**, **Woolf H**, **Musaeus N**, **Krinsky NI**, **Russell RM**, **Yeum KJ**.

Jean Mayer USDA-Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111, USA.

BACKGROUND: Oxidative stress has been implicated in the pathogenesis of chronic diseases related to aging such as cancer and cardiovascular disease. Carotenoids could be a part of a protective strategy to minimize oxidative damage in vulnerable populations, such as the elderly. OBJECTIVE: Our aim was to determine the protective effect of carotenoids against DNA damage. DESIGN: A randomized, double-blind, placebo-controlled intervention study was conducted. Thirty-seven healthy, nonsmoking postmenopausal women aged 50-70 y were randomly assigned to 1 of 5 groups and were instructed to consume a daily dose of mixed carotenoids (beta-carotene, lutein, and lycopene; 4 mg each), 12 mg of a single carotenoid (beta-carotene, lutein, or lycopene), or placebo for 56 d. Plasma carotenoid concentrations were analyzed by using HPLC, and lymphocyte DNA damage was measured by using a single-cell gel electrophoresis (comet) assay. RESULTS: At day 57, all carotenoid-supplemented groups showed significantly lower endogenous DNA damage than at baseline ($P < 0.01$), whereas the placebo group did not show any significant change. Significantly less ($P < 0.05$) endogenous DNA damage was found as early as day 15 in the mixed carotenoid ($P < 0.01$) and beta-carotene ($P < 0.05$) groups. CONCLUSIONS: The results indicate that carotenoid supplementation decreases DNA damage and that a combination of carotenoids (4 mg each of lutein, beta-carotene, and lycopene), an intake that can be achieved by diet, or a larger dose (12 mg) of individual carotenoids exerts protection against DNA damage.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 16400064 [PubMed - indexed for MEDLINE]

Mol Aspects Med. 2005 Dec;26(6):459-516. Epub 2005 Nov 23.

Carotenoid actions and their relation to health and disease.

Krinsky NI, **Johnson EJ**.

Department of Biochemistry, School of Medicine, Tufts University, 136 Harrison Avenue, Boston, MA 02111-1837, USA. norman.krinsky@tufts.edu

Based on extensive epidemiological observation, fruits and vegetables that are a rich source of carotenoids are thought to provide health benefits by decreasing the risk of various diseases, particularly certain cancers and eye diseases. The carotenoids that have been most studied in this regard are beta-carotene, lycopene, lutein and zeaxanthin. In part, the beneficial effects of carotenoids are thought to be due to their role as antioxidants. beta-Carotene may have added benefits due its ability to be converted to vitamin A. Additionally, lutein and zeaxanthin may be protective in eye disease because they absorb damaging blue light that enters the eye. Food sources of these compounds include a variety of fruits and vegetables, although the primary sources of lycopene are tomato and tomato products. Additionally, egg yolk is a highly bioavailable source of lutein and zeaxanthin. These carotenoids are available in supplement form. However, intervention trials with large doses of beta-carotene found an adverse effect on the incidence of lung cancer in smokers and workers exposed to asbestos. Until the efficacy and safety of taking supplements containing these nutrients can be determined, current dietary recommendations of diets high in fruits and vegetables are advised.

Publication Types:

- Review

PMID: 16309738 [PubMed - indexed for MEDLINE]

Oncol Rep. 2005 Nov;14(5):1385-92.

Identification of carotenoids in ovarian tissue in women.

Czeczuga-Semeniuk E, **Wolczynski S**.

Department of Gynaecological Endocrinology, Medical University of Bialystok, M. Sklodowskiej-Curie 24A, 15-267 Bialystok, Poland. czeczuga@wp.pl

Epidemiological and clinical studies have revealed that vitamin A and its derivatives (carotenoids and retinoids) can reduce the risk of ovarian tumours and may have a role in the metabolism of patients with ovarian cancer. The aim of the study was identification and quantitative assessment of carotenoids found in nature, mainly of provitamin A group, in the tissue material obtained from patients with different lesions of the ovaries. Material for analysis was obtained from 100 women, aged 16-74, operated on for ovarian tumours in the Department of Gynaecology. Carotenoid pigments were separated using column chromatography, thin-layer chromatography and high-performance liquid chromatography. In the tissue material subjected to analysis, 14 carotenoids were identified, including provitamin A carotenoids; beta-carotene, beta-cryptoxanthin, echinenone and hydroxyechinenone. alpha-carotene was not found. In the whole group of pathological lesions, the total carotenoid content was relatively low (mean 1.717 microg/g tissue) and the mean content of provitamin A carotenoids was 17.28%. These results are similar to results obtained in the group of normal ovarian tissue. In the group of benign mucinous tumours (1.042 microg/g tissue) and tumours in the thecoma-fibroma group (1.328 microg/g tissue) and dysgerminoma group (1.279 microg/g tissue), the total carotenoid content was lower. Only in the endometriosis group was this value higher (2.185 microg/g tissue). Epoxy carotenoids; lutein epoxide, violaxanthin and mutatoxanthin were predominant (in %). Irrespective of histological classification, beta-carotene, beta-cryptoxanthin, lutein, lutein epoxide, violaxanthin and mutatoxanthin were identified in all tissue examined. Antheraxanthin was isolated in all tissue except for normal ovarian tissue, serous malignant and mucinous benign and malignant tumours, endometrioid malignant tumours, dermoid cysts, corpus luteum cysts and simple cysts. Hydroxyechinenone was isolated sporadically. Only in one case was capsanthin isolated. Carotenoids act as chemopreventive agents, irrespective of whether they are finally transformed into vitamin A, and may represent a potentially powerful alternative to present chemotherapeutic approaches to the treatment of ovarian cancer.

PMID: 16211314 [PubMed - indexed for MEDLINE]

Biochim Biophys Acta. 2005 May 30;1740(2):206-14. Epub 2005 Feb 5.

The effect of beta-carotene and its derivatives on cytotoxicity, differentiation, proliferative potential and apoptosis on the three human acute leukemia cell lines: U-937, HL-60 and TF-1.

Sacha T, **Zawada M**, **Hartwich J**, **Lach Z**, **Polus A**, **Szostek M**, **Zdzi Owska E**, **Libura M**, **Bodzioch M**, **Dembińska-Kieć A**, **Skotnicki AB**, **Góralczyk R**, **Wertz K**, **Riss G**, **Moele C**, **Langmann T**, **Schmitz G**.

Chair and Department of Haematology, Jagiellonian University Medical College, ul. Kopernika 17, 31-501 Cracow, Poland. mmsacha@cyf-kr.edu.pl

The influence of beta-carotene (BC) and its derivatives on differentiation, proliferation and apoptosis in three human acute leukemia cell lines was studied. We investigated: (i) the cellular uptake of BC, (ii) the cytotoxicity, (iii) the effect on cell cycle progression and/or apoptosis. The dose- and time-dependent pattern of cellular BC uptake in all studied cell lines was seen. We did not observe any cytotoxic effect of BC and ATRA in the chosen concentrations. There was only limited effect of BC on gene expression. The microarrray analysis of U-937 cell line exposed to BC for 72 h showed an increased expression of BAX gene. This finding was confirmed by real-time Q-PCR analysis, and supported by a flow cytometry apoptosis tests. We did not observe any influence of studied components on cellular proliferation. The induction of differentiation after incubation with ATRA in HL-60 cells was noted. The induction of cellular apoptosis by BC was seen in all studied cell lines. We demonstrated that BC used in the concentrations achievable in vivo does not affect the proliferation and differentiation process of the studied leukemic cell lines, but can influence and enhance the apoptosis by modulating the expression of the regulatory genes.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 15949688 [PubMed - indexed for MEDLINE]

Eur J Cancer. 2007 Nov;43(17):2590-601. Epub 2007 Oct 1.

beta-Carotene induces apoptosis and up-regulates peroxisome proliferator-activated receptor gamma expression and reactive oxygen species production in MCF-7 cancer cells.

Cui Y, **Lu Z**, **Bai L**, **Shi Z**, **Zhao WE**, **Zhao B**.

Chemical Engineering College, Zhengzhou University, No. 100 Science Road, Zhengzhou, 450001, People's Republic of China.

Although the pharmacological role of beta-carotene in the prevention and treatment of many cancer cells has received increasing attention, the molecular mechanisms underlying such chemopreventive activity are not clear. Since peroxisome proliferator-activated receptor gamma (PPAR-gamma) has been implicated in regulating breast cancer cell differentiation and apoptosis, the effects of beta-carotene on the PPAR-gamma-mediated pathway and its association with reactive oxygen species production in MCF-7 cells were investigated in the present study. The results demonstrated that beta-carotene significantly increased PPAR-gamma mRNA and protein levels in time-dependent manner. In addition, beta-carotene increased the cyclin-dependent kinase inhibitor p21(WAF1/CIP1) expression and decreased the prostanoid synthesis rate-limiting enzyme cyclooxygenase-2 expression. 2-chloro-5-nitro-N-phenylbenzamide (GW9662), an irreversible PPAR-gamma antagonist, partly attenuated the cell death caused by beta-carotene. Further, reactive oxygen species (ROS) production was induced by beta-carotene, resulting in mitochondrial dysfunction and cytochrome C release. Reduced glutathione (GSH) treatment decreases the intracellular ROS and prevents cytochrome C release and cell apoptosis induced by beta-carotene. In total, these observations suggest that the synergistic effect of PPAR-gamma expression and ROS production may account for beta-carotene-mediated anticancer activities.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17911009 [PubMed - indexed for MEDLINE]

J Nutr Biochem. 2007 Oct;18(10):667-75. Epub 2007 Mar 21.

Carotenoids suppress proliferating cell nuclear antigen and cyclin D1 expression in oral carcinogenic models.

Cheng HC, **Chien H**, **Liao CH**, **Yang YY**, **Huang SY**.

Orthodontic Department, Taipei Medical University Hospital, Taipei Medical University, Taipei 110, Taiwan.

The purpose of this study was to investigate the chemopreventive effect of carotenoids on proliferating cell nuclear antigen (PCNA) and cyclin D(1) expression in betel (Areca catechu) quid extract (BQE)-induced hamster oral cancer and human KB cell models, respectively. In the in vivo animal study, 41 hamsters were divided into six groups and treated with 0.3 ml of 0.5% 9,10-dimethyl-1,2-benz[a]-anthracene, BQE, alpha-tocopherol, beta-carotene, lycopene, lutein and mixed carotenoids for 12 weeks. After treatment, the pouches were excised and graded using an immunohistochemical assay of PCNA. In the in vitro cell experiment, KB cells were cultured, and the inhibitory effect of carotenoids (beta-carotene, lycopene and lutein) on cell proliferation was evaluated. Cyclin D(1) and PCNA were evaluated in terms of cell differentiation. In the results, most of the animal lesions showed no overexpression of PCNA. However, in dysplastic lesions, PCNA expressions by the beta-carotene, lutein, lycopene, mixed and vitamin E groups were less than that of the control group. In papilloma lesions, PCNA expressions by the beta-carotene, mixed and vitamin E groups were less severe than that of the control group. PCNA expression by the vitamin E-treated group was less severe than that of the control group. No carcinoma was found in the lycopene or mixed groups. In the cell study, all carotenoids exerted a significant inhibitory effect on KB cell proliferation. Although lycopene suppressed KB cell proliferation at the G(0)/G(1) phase with a significant decrease in PCNA expression, beta-carotene and lutein possessed less of an inhibitory effect and even exhibited elevated cell proliferation at the G(2)/M phase. These results indicate that different carotenoids present various suppressive abilities against PCNA and cyclin D(1) expressions in cell proliferation. In conclusion, carotenoids suppressed the carcinogenesis of induced hamster oral cancer and a cancer cell line by acting as a suppressor which inhibited the expressions of PCNA and cyclin D(1).

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17369034 [PubMed - indexed for MEDLINE]

Int J Cancer. 2009 Jun 15;124(12):2929-37.

Dietary carotenoids and the risk of invasive breast cancer.

Mignone LI, **Giovannucci E**, **Newcomb PA**, **Titus-Ernstoff L**, **Trentham-Dietz A**, **Hampton JM**, **Willett WC**, **Egan KM**.

Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA. lmignone@hsph.harvard.edu

Certain classes of vitamins and nutrients found in fruits and vegetables have been of particular interest in relation to cancer prevention, owing to their potential anticarcinogenic properties. We examined the association between certain fruits, vegetables, carotenoids, and vitamin A and breast cancer risk in a large population-based case-control study of women residing in the states of Massachusetts, New Hampshire and Wisconsin. The study was comprised of 5,707 women with incident invasive breast cancer (2,363 premenopausal women and 3,516 postmenopausal women) and 6,389 population controls (2,594 premenopausal women and 3,516 postmenopausal women). In an interview, women were asked about their intake of carotenoid rich fruits and vegetables 5 years prior to a referent date. An inverse association observed among premenopausal women was for high levels of vitamin A (OR: 0.82, 95% CI: 0.68-0.98, p for trend = 0.01), beta-carotene (OR: 0.81, 95% CI 0.68-0.98, p for trend = 0.009), alpha-carotene (OR: 0.82, 95% CI: 0.68-0.98, p for trend = 0.07) and lutein/zeaxanthin (OR: 0.83, 95% CI 0.68-0.99, p for trend = 0.02). An inverse association was not observed among postmenopausal women. Among premenopausal women who reported ever smoking, these results were stronger than among never smokers, although tests for interaction were not statistically significant. Results from this study are comparable to previous prospective studies, and suggest that a high consumption of carotenoids may reduce the risk of premenopausal but not postmenopausal breast cancer, particularly among smokers. Copyright 2008 UICC.

Publication Types:

- Comparative Study
- Multicenter Study
- Research Support, N.I.H., Extramural

PMID: 19330841 [PubMed - indexed for MEDLINE]

Cancer Causes Control. 2009 Jul;20(5):699-711. Epub 2008 Dec 16.

Antioxidant vitamins and the risk of endometrial cancer: a dose-response meta-analysis.

Bandera EV, **Gifkins DM**, **Moore DF**, **McCullough ML**, **Kushi LH**.

The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, 195 Little Albany St, New Brunswick, NJ 08903, USA. elisa.bandera@umdnj.edu

Antioxidant vitamins may reduce cancer risk by limiting oxidative DNA damage. To summarize and quantify the current epidemiologic evidence of an association between antioxidant vitamin intake and endometrial cancer, we conducted a systematic literature review and meta-analysis. One cohort and 12 case-control studies presenting relevant risk estimates were identified by conducting bibliographical searches through June 2008. Dose-response meta-analyses were conducted for beta-carotene, vitamin C, and vitamin E from food sources. Intake from supplements was not considered in the meta-analyses because of the few studies that reported relevant information. Based on case-control data, the random-effects summary odds ratios (OR) were, for beta-carotene: 0.88 (95% CI: 0.79-0.98) per 1,000 mcg/1,000 kcal (I2: 77.7%; $p < 0.01$); for vitamin C: 0.85 (95% CI: 0.73-0.98) per 50 mg/1,000 kcal (I2: 66.1%; $p < 0.01$); and, for vitamin E: 0.91 (95% CI: 0.84-0.99) per 5 mg/1,000 kcal (I2: 0.0%; p: 0.45). In contrast, the only prospective study identified provided little indication of an association. Although the current case-control data suggest an inverse relationship of endometrial cancer risk with dietary intakes of beta-carotene, vitamin C, and vitamin E from food sources, additional studies are needed, particularly cohort studies, to confirm an association.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 19083131 [PubMed - in process]

Ann Oncol. 2009 Jan;20(1):160-5. Epub 2008 Jul 31.

Dietary intake of selected micronutrients and gastric cancer risk: an Italian case-control study.

Pelucchi C, **Tramacere I**, **Bertuccio P**, **Tavani A**, **Negri E**, **La Vecchia C**.

Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.
pelucchi@marionegri.it

BACKGROUND: A high consumption of non-starchy vegetables and fruits likely decreases the risk of gastric cancer, but no specific constituent of plant foods has been consistently identified to explain this association. PATIENTS AND METHODS: We considered several micronutrients and minerals in an Italian case-control study conducted between 1997 and 2007, including 230 patients with incident, histologically confirmed gastric cancer and 547 matched controls, admitted with acute conditions. Micronutrients computation was based on a validated and reproducible food frequency questionnaire, through an Italian food composition database. We estimated odds ratios (ORs) using conditional logistic regression, adjusted for energy intake and selected covariates. RESULTS: We found decreased ORs for the highest versus lowest quartile of vitamin E (OR=0.50), alpha-carotene (OR=0.52) and beta-carotene (OR=0.42) intake. Gastric cancer was directly associated with sodium, with ORs of 2.22 for the second, 2.56 for the third and 2.46 for the fourth quartile of intake. No significant relation emerged with iron, calcium, potassium, zinc, vitamin C, thiamin, riboflavin, niacin, vitamin B6, folate, vitamin D, retinol, beta-cryptoxanthin, lycopene and lutein plus zeaxanthin. CONCLUSIONS: Our data support a favourable effect on gastric cancer of vitamin E and selected carotenoids and a detrimental effect of sodium even at intermediate levels of intake.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18669867 [PubMed - indexed for MEDLINE]

PMCID: PMC2638677 [Available on 2010/01/01]

Carcinogenesis. 2008 May;29(5):1042-8. Epub 2008 Mar 13.

Plasma levels of carotenoids, retinol and tocopherol and the risk of gastric cancer in Japan: a nested case-control study.

Persson C, **Sasazuki S**, **Inoue M**, **Kurahashi N**, **Iwasaki M**, **Miura T**, **Ye W**, **Tsugane S**; **JPHC Study Group**.Collaborators (100).

Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku 104-0045, Tokyo, Japan.

Fruits and vegetables have been suggested to confer protection against diseases such as cancer through the effects of antioxidants, often represented by carotenoids. We investigated the impact of carotenoids, retinol and tocopherol on gastric cancer development in a large nested case-control study among Japanese with known Helicobacter pylori infection status. A total of 36 745 subjects aged 40-69 in the Japan Public Health Center-based Prospective Study who responded to the baseline questionnaire and provided blood samples in 1990-1995 were followed until 2004. Plasma levels of carotenoids in 511 gastric cancer cases and 511 matched controls were measured by high-performance liquid chromatography. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were estimated using conditional logistic regression models. Plasma level of beta-carotene was inversely associated with the risk of gastric cancer (compared with the lowest quartile: OR = 0.63, 95% CI = 0.31-0.75; OR = 0.48, 95% CI = 0.31-0.75 and OR = 0.46, 95% CI = 0.28-0.75, for quartile 2, 3 and 4, respectively, P(trend) < 0.01). Inverse associations were evident in men for alpha-carotene (P(trend) = 0.04) and beta-carotene (P(trend) < 0.01), but not in women, who had relatively higher plasma levels compared with men. We found no statistically significant association between plasma levels of lutein/zeaxanthin, lycopene, retinol, alpha- or gamma-tocopherol and gastric cancer risk. Our findings suggest that those who have very low plasma levels of alpha-carotene and beta-carotene are at a higher risk of gastric cancer.
Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18339681 [PubMed - indexed for MEDLINE]

Urology. 2008 Sep;72(3):633-7. Epub 2008 Feb 15.

The Men's Eating and Living (MEAL) study: a Cancer and Leukemia Group B pilot trial of dietary intervention for the treatment of prostate cancer.

Parsons JK, **Newman V**, **Mohler JL**, **Pierce JP**, **Paskett E**, **Marshall J**; **Cancer and Leukemia Group B**.

Moores Cancer Center, University of California-San Diego, La Jolla, California, USA. jkparsons@ucsd.edu

OBJECTIVES: To evaluate the feasibility of implementing a diet-based intervention in men with prostate cancer. METHODS: Seventy-four men aged 50 to 80 years with biopsy-proven adenocarcinoma of the prostate were randomized to receive either telephone-based dietary counseling or standardized, written nutritional information. Telephone dietary counseling targets included increased intakes of vegetables (particularly cruciferous vegetables and tomato products), whole grains, and beans/legumes. Dietary intakes and plasma carotenoid levels were assessed at baseline and at 6 months' follow-up. RESULTS: In the intervention arm, mean daily intakes of total vegetables, crucifers, tomato products, and beans/legumes increased by 76%, 143%, 292%, and 95%, respectively, whereas fat intake decreased by 12% (P = 0.02). In the control arm, there were no significant changes in mean intakes of total vegetables, tomato products, crucifers, beans/legumes, or fat. Similarly, in the intervention arm, mean plasma levels of alpha-carotene, beta-carotene, lutein, lycopene, and total carotenoids increased by 33%, 36%, 19%, 30%, and 26%, respectively (P <0.05). In the control arm, there were no significant changes in plasma levels of alpha- or beta-carotene, lutein, lycopene, or total carotenoids. CONCLUSIONS: Telephone-based dietary counseling increases vegetable intake, decreases fat intake, and significantly increases plasma levels of potentially anticarcinogenic carotenoids in men with prostate cancer. These data support the feasibility of implementing clinical trials of dietary intervention in men with prostate cancer.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18280560 [PubMed - indexed for MEDLINE]

J Biochem Mol Biol. 2007 Nov 30;40(6):1009-15.

Cell cycle regulation and induction of apoptosis by beta-carotene in U937 and HL-60 leukemia cells.

Upadhyaya KR, **Radha KS**, **Madhyastha HK**.

Department of Applied Physiology, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.

In this communication, we report the efficacy of beta-carotene towards differentiation and apoptosis of leukemia cells. Dose (20 microM) and time dependence (12 h) tests of beta- carotene showed a higher magnitude of decrease (significance $p < 0.05$) in cell numbers and cell viability in HL-60 cells than U937 cells but not normal cell like Peripheral blood mononuclear cell (PBMC). Microscopical observation of beta-carotene treated cells showed a distinct pattern of morphological abnormalities with inclusion of apoptotic bodies in both leukemia cell lines. When cells were treated with 20 microM of beta-carotene, total genomic DNA showed a fragmentation pattern and this pattern was clear in HL-60 than U937 cells. Both the cell lines, on treatment with beta- carotene, showed a clear shift in G(1) phase of the cell cycle. In addition the study also revealed anti-oxidant properties of beta-carotene since there was reduction in relative fluorescent when treated than the control at lower concentration. Collectively this study shows the dual phenomenon of apoptosis and differentiation of leukemia cells on treatment with beta-carotene.

PMID: 18047798 [PubMed - indexed for MEDLINE]

Br J Nutr. 2007 Oct;98 Suppl 1:S127-32.

Nutrition and immunity in cancer.

Valdés-Ramos R, **Benítez-Arciniega AD**.

Facultad de Medicina, Universidad Autónoma del Estado de México, Jesús Carranza esq. Paseo Tollocan, Col. Moderna de la Cruz, Toluca, Estado de México, 50180, Mexico. rycramos@uaemex.mx

The purpose of this article is to give a general overview of the effects of nutrition on the development of cancer as well as part of a therapeutic approach. There is much evidence that diet and lifestyle can alter the risk of cancer development as is the case for many other chronic diseases. This may be through a direct action on the immune system, either by enhancing or suppressing it, as well as on the development of the tumour itself, by modulating gene expression or by antioxidant activity. Protective effects can be achieved by adequate intakes of vitamins A and C, beta-carotene, selenium and n-3 fatty acids among others, while negative effects are found mainly with high intakes of n-6 and saturated fatty acids. Weight gain, obesity and lack of regular physical activity have also been associated with an increased risk of cancer. The protective effects are best observed when adequate diet and lifestyle are present together. With respect to the therapeutic role of nutrition in cancer, it has been observed that the use of pre- or post-operative enteral or parenteral nutrition may improve patients' survival rates and quality of life; however, more research is needed in this particular area. Breast, colon, rectum, prostate, stomach and lung are the types of cancer most commonly associated with diet or dietary components.

Publication Types:

- Review

PMID: 17922950 [PubMed - indexed for MEDLINE]

J Cancer Res Ther. 2006 Jan-Mar;2(1):24-7.

Brain tumor and role of beta-carotene, a-tocopherol, superoxide dismutase and glutathione peroxidase.

Aggarwal S, **Subberwal M**, **Kumar S**, **Sharma M**.

Department of Biochemistry, Maulana Azad Medical College, New Delhi, India.

The erythrocyte levels of the antioxidant enzymes SOD and GPx, and serum levels of antioxidants vitamins beta-carotene and beta-tocopherol were estimated in various types of brain tumors, and were compared with the levels in controls. Statistically significant (P<.001) diminished levels of beta-carotene, beta-tocopherol, SOD and GPx, were observed in all the brain tumor patients as compared to controls. Malignant tumor also showed a relative decrease in antioxidant levels as compared to benign tumors. Comparison of histopathological sections of brain tumors also suggested a inverse relationship between antioxidant level and grades of malignancy. Marked decrease in antioxidant levels may have a role in genesis of considerable oxidative stress in brain tumors. Furthermore, the degree of decline in antioxidant levels may indicate severity of malignancy in brain tumors.

PMID: 17998669 [PubMed - indexed for MEDLINE]

Eur J Cancer. 2007 Nov;43(17):2590-601. Epub 2007 Oct 1.

beta-Carotene induces apoptosis and up-regulates peroxisome proliferator-activated receptor gamma expression and reactive oxygen species production in MCF-7 cancer cells.

Cui Y, **Lu Z**, **Bai L**, **Shi Z**, **Zhao WE**, **Zhao B**.

Chemical Engineering College, Zhengzhou University, No. 100 Science Road, Zhengzhou, 450001, People's Republic of China.

Although the pharmacological role of beta-carotene in the prevention and treatment of many cancer cells has received increasing attention, the molecular mechanisms underlying such chemopreventive activity are not clear. Since peroxisome proliferator-activated receptor gamma (PPAR-gamma) has been implicated in regulating breast cancer cell differentiation and apoptosis, the effects of beta-carotene on the PPAR-gamma-mediated pathway and its association with reactive oxygen species production in MCF-7 cells were investigated in the present study. The results demonstrated that beta-carotene significantly increased PPAR-gamma mRNA and protein levels in time-dependent manner. In addition, beta-carotene increased the cyclin-dependent kinase inhibitor p21(WAF1/CIP1) expression and decreased the prostanoid synthesis rate-limiting enzyme cyclooxygenase-2 expression. 2-chloro-5-nitro-N-phenylbenzamide (GW9662), an irreversible PPAR-gamma antagonist, partly attenuated the cell death caused by beta-carotene. Further, reactive oxygen species (ROS) production was induced by beta-carotene, resulting in mitochondrial dysfunction and cytochrome C release. Reduced glutathione (GSH) treatment decreases the intracellular ROS and prevents cytochrome C release and cell apoptosis induced by beta-carotene. In total, these observations suggest that the synergistic effect of PPAR-gamma expression and ROS production may account for beta-carotene-mediated anticancer activities.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17911009 [PubMed - indexed for MEDLINE]

Integr Cancer Ther. 2007 Sep;6(3):258-70.

Beta-carotene inhibits tumor-specific angiogenesis by altering the cytokine profile and inhibits the nuclear translocation of transcription factors in B16F-10 melanoma cells.

Guruvayoorappan C, **Kuttan G**.

Department of Immunology, Amala Cancer Research Centre, Amala Nagar, Kerala State, India.

Angiogenesis is the formation of new blood vessels out of the preexisting vascular network and involves a sequence of events that are of key importance in a broad array of physiological and pathological processes. The growth of tumor and metastasis are dependent on the formation of new blood vessels. The present study therefore aims at evaluating the antiangiogenic effect of beta-carotene using in vivo and in vitro models. Male C57BL/6 mice as well as B16F-10 cells were used for the experimental study. The in vivo study includes the inhibitory effect of beta-carotene on the formation of tumor-directed capillaries. Rat aortic ring assay, human umbilical vein endothelial cell proliferation, migration, and tube formation are used for assessing the in vitro antiangiogenic effect of beta-carotene. The differential regulation of proinflammatory cytokines as well as the inhibitory effect of beta-carotene on the activation and nuclear translocation of transcription factors are also assessed. Beta-carotene treatment significantly reduces the number of tumor-directed capillaries accompanied by altered serum cytokine levels. Beta-carotene is able to inhibit proliferation, migration, and tube formation of endothelial cells. Beta-carotene treatment downregulates the expression of matrix metalloproteinase (MMP)-2, MMP-9, prolyl hydroxylase, and lysyl oxidase gene expression and upregulates the expression of tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2. The study reveals that beta-carotene treatment could alter proinflammatory cytokine production and could inhibit the activation and nuclear translocation of p65, p50, c-Rel subunits of nuclear factor-kappa B, and other transcription factors such as c-fos, activated transcription factor-2, and cyclic adenosine monophosphate response element-binding protein in B16F-10 melanoma cells. These observations show that beta -carotene exerts its antiangiogenic effect by altering the cytokine profile and could inhibit the activation and nuclear translocation of transcription factors.

Publication Types:

- In Vitro

PMID: 17761639 [PubMed - indexed for MEDLINE]

Beta Carotene and Eye Health

Public Health Nutr. 2002 Apr;5(2):347-52.

The intake of carotenoids in an older Australian population: The Blue Mountains Eye Study.

Manzi F, **Flood V**, **Webb K**, **Mitchell P**.

University of Sydney, Department of Public Health & Community Medicine, Westmead Hospital, Australia.

OBJECTIVE: To describe the distribution of carotenoid intakes and important food sources of carotenoids in the diet of a representative population of older Australians. DESIGN: Population-based cohort study. SETTING: Two post-code areas in the Blue Mountains, west of Sydney, Australia. SUBJECTS: We studied 2012 (86%) of the 2334 participants aged 55+ years attending the 5-year follow-up of the cross-sectional Blue Mountains Eye Study (BMES), who completed a detailed semi-quantitative food-frequency questionnaire. The intakes for five carotenoids were studied: alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein and zeaxanthin combined, and lycopene. RESULTS: The mean intake per day for each carotenoid was: alpha-carotene, 2675 microg; beta carotene equivalents, 7301 microg; beta-cryptoxanthin, 299 microg; lutein and zeaxanthin, 914 microg; lycopene, 3741 microg; retinol, 653 microg; total vitamin A, 1872 microg retinol equivalents. beta-Carotene equivalents contribute a substantial proportion of total vitamin A intake (65%) in this population. Women had slightly higher intakes than men for alpha-carotene, beta-carotene equivalents, and lutein and zeaxanthin ($P < 0.05$). Carrots and pumpkin were the main contributors to alpha-carotene and beta-carotene equivalent intakes. Orange juice, oranges and papaw were the main contributors to beta-cryptoxanthin intake. Broccoli, green beans and oranges contributed substantially to lutein and zeaxanthin intake. The main contributors to lycopene intake were tomatoes and bolognaise sauce. CONCLUSIONS: Vitamin A intake in this population is high relative to the Australian Recommended Dietary Intake. Carotenoid intakes, particularly beta-carotene, make a substantial contribution, particularly from fruit and vegetables. This study provides important information as a basis for examining associations between dietary carotenoid intake and eye disease in the BMES.

PMID: 12020387 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2008 Jun;87(6):1899-905.

Antioxidant nutrient intake and the long-term incidence of age-related cataract: the Blue Mountains Eye Study.

Tan AG, **Mitchell P**, **Flood VM**, **Burlutsky G**, **Rochtchina E**, **Cumming RG**, **Wang JJ**.

Department of Ophthalmology, Centre for Vision Research, Westmead Millennium Institute, University of Sydney, Sydney, NSW, Australia.

BACKGROUND: Oxidative stress has been implicated in cataractogenesis. Long-term intake of antioxidants may offer protection against cataract. OBJECTIVE: We investigated relations between antioxidant nutrient intakes measured at baseline and the 10-y incidence of age-related cataract. DESIGN: During 1992-1994, 3654 persons aged >or=49 y attended baseline examinations of the Blue Mountains Eye Study (82.4% response). Of these persons, 2464 (67.4%) participants were followed >or=1 time after the baseline examinations (at either 5 or 10 y). At each examination, lens photography was performed and questionnaires were administered, including a 145-item semiquantitative food-frequency questionnaire. Antioxidants, including beta-carotene, zinc, and vitamins A, C, and E, were assessed. Cataract was assessed at each examination from lens photographs with the use of the Wisconsin Cataract Grading System. Nuclear cataract was defined for opacity greater than standard 3. Cortical cataract was defined as cortical opacity >or= 5% of the total lens area, and posterior subcapsular (PSC) cataract was defined as the presence of any such opacity. RESULTS: Participants with the highest quintile of total intake (diet + supplements) of vitamin C had a reduced risk of incident nuclear cataract [adjusted odds ratio (OR): 0.55; 95% CI: 0.36, 0.86]. An above-median intake of combined antioxidants (vitamins C and E, beta-carotene, and zinc) was associated with a reduced risk of incident nuclear cataract (OR: 0.51; 95% CI: 0.34, 0.76). Antioxidant intake was not associated with incident cortical or PSC cataract. CONCLUSION: Higher intakes of vitamin C or the combined intake of antioxidants had long-term protective associations against development of nuclear cataract in this older population.

PMID: 18541583 [PubMed - indexed for MEDLINE]

Eye. 2008 Jun;22(6):751-60. Epub 2008 Apr 18.

Antioxidant supplements to prevent or slow down the progression of AMD: a systematic review and meta-analysis.

Evans J.

International Centre for Eye Health, London School of Hygiene and Tropical Medicine (LSHTM), London, UK. jennifer.evans@lshtm.ac.uk

INTRODUCTION: The aim of this review was to examine the evidence as to whether antioxidant vitamin or mineral supplements prevent the development of AMD or slow down its progression. METHODS: Randomised trials comparing antioxidant vitamin and/or mineral supplement to control were identified by systematic electronic searches (updated August 2007) and contact with investigators. Data were pooled after investigating clinical and statistical heterogeneity. RESULTS: There was no evidence that antioxidant (vitamin E or beta-carotene) supplementation prevented AMD. A total of 23 099 people were randomised in three trials with treatment duration of 4-12 years; pooled risk ratio=1.03 (95% CI, 0.74-1.43). There was evidence that antioxidant (beta-carotene, vitamin C, and vitamin E) and zinc supplementation slowed down the progression to advanced AMD and visual acuity loss in people with signs of the disease (adjusted odds ratio=0.68, 95% CI, 0.53-0.87 and 0.77, 95% CI, 0.62-0.96, respectively). The majority of people were randomised in one trial (AREDS, 3640 people randomised). There were seven other small trials (total randomised 525). CONCLUSIONS: Current evidence does not support the use of antioxidant vitamin supplements to prevent AMD. People with AMD, or early signs of the disease, may experience some benefit from taking supplements as used in the AREDS trial. Potential harms of high-dose antioxidant supplementation must be considered. These may include an increased risk of lung cancer in smokers (beta-carotene), heart failure in people with vascular disease or diabetes (vitamin E) and hospitalisation for genitourinary conditions (zinc).

Publication Types:

- Meta-Analysis
- Review

PMID: 18425071 [PubMed - indexed for MEDLINE]

Invest Ophthalmol Vis Sci. 2008 Aug;49(8):3328-35. Epub 2008 Apr 17.

Blood levels of vitamin C, carotenoids and retinol are inversely associated with cataract in a North Indian population.

Dherani M, **Murthy GV**, **Gupta SK**, **Young IS**, **Maraini G**, **Camparini M**, **Price GM**, **John N**, **Chakravarthy U**, **Fletcher AE**.

Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom.

PURPOSE: To examine the association of blood antioxidants with cataract. METHODS: Cross-sectional study of people aged >or=50 years identified from a household enumeration of 11 randomly sampled villages in North India. Participants were interviewed for putative risk factors (tobacco, alcohol, biomass fuel use, sunlight exposure, and socioeconomic status) and underwent lens photography and blood sampling. Lens photographs (nuclear, cortical, and posterior subcapsular) were graded according to the Lens Opacities Classification System (LOCS II). Cataract was defined as LOCS II grade >or=2 for any opacity or ungradable, because of dense opacification or history of cataract surgery. People without cataract were defined as LOCS II <2 on all three types of opacity, with absence of previous surgery. RESULTS: Of 1443 people aged >or=50 years, 94% were interviewed, 87% attended an eye examination, and 78% gave a blood sample; 1112 (77%) were included in the analyses. Compared with levels in Western populations, antioxidants were low, especially vitamin C. Vitamin C was inversely associated with cataract. Odds ratios (OR) for the highest (>or=15 micromol/L) compared with the lowest (<or=6.3 micromol/L) tertile were 0.64, (95% confidence interval [CI] 0.48-0.85; P < 0.01). Tertiles of zeaxanthin (P < 0.03), alpha-carotene (P < 0.05), and retinol (P < 0.02) were associated with decreased odds of cataract. In analysis of continuous data, significant inverse associations were found for vitamin C, zeaxanthin, lutein, lycopene, alpha- and beta-carotene, and beta-cryptoxanthin, but not for alpha- or gamma-tocopherol. CONCLUSIONS: Inverse associations were found between cataract and blood antioxidants in an antioxidant-depleted study sample.

Publication Types:

- Multicenter Study
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 18421094 [PubMed - indexed for MEDLINE]

Clin Nutr. 2008 Jun;27(3):464-72. Epub 2008 Mar 14.

Dietary and nutritional biomarkers of lens degeneration, oxidative stress and micronutrient inadequacies in Indian cataract patients.

Tarwadi KV, **Chiplonkar SA**, **Agte V**.

Biometry and Nutrition, Agharkar Research Institute, G.G. Agarkar Road, Pune 411004, India.

BACKGROUND & AIMS: Habitual food and nutrient intakes of 140 Indian cataract patients and 100 age- and sex-matched controls (50-75 years), from high income group and low income groups, were assessed. METHODS: Food intake was recorded by food frequency questionnaire and data were examined for linkages with blood/lens parameters of oxidative stress through a case-control study. RESULTS: Intake of animal foods and fried snacks was significantly higher while vegetables, green leafy vegetables, fruit, tea and micronutrient intakes were lower in patients than in controls ($p<0.001$). Lens oxidative stress and opacity showed a significant negative association with fruit intake ($p<0.05$). Multiple regression analysis indicated association of intakes of iron, beta-carotene, ascorbic acid, tannic acid and inositol pentaphosphate with plasma oxidative stress ($p<0.01$) and association of intakes of iron, ascorbic acid and inositol triphosphate with lens oxidative stress ($p<0.01$). Weighted least square regression for lens opacity revealed that intakes of ascorbic acid, folic acid and inositol pentaphosphate explained 59.7% of the total variation ($p<0.01$). CONCLUSIONS: Dietary deficiency of antioxidant micronutrients was greater for patients than controls. Deficiency of beta-carotene, ascorbic acid, folic acid, iron, phytate and polyphenols increased oxidative stress in blood and lens.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18342406 [PubMed - indexed for MEDLINE]

Orv Hetil. 2007 Dec 2;148(48):2259-68.

[Metabolic therapy for early treatment of age-related macular degeneration]

[Article in Hungarian]

Fehér J, **Kovács B**, **Kovács I**, **Schvöller M**, **Corrado Balacco G**.
La Sapienza Tudományegyetem, Szemészeti Klinika, Roma. j.feher@libero.it

Currently, age-related macular degeneration is one of the most common eye diseases causing severe and permanent loss of vision. This disease is estimated to affect approximately 300-500 thousand Hungarians. While earlier no treatment was available, in the recent decade an antioxidant therapy became very popular using combinations of high dosage antioxidant vitamins C, E, beta carotene and zinc. Based on theoretical concepts and mostly in vitro experiences, this combination was thought to be effective through neutralizing reactive oxygen species. According to a large clinical trial (AREDS) it reduced progression of intermediate state disease to advanced state, but did not influence early disease. This original combination, due to potential severe side effects, is not on the market anymore. However, the efficacy of modified formulas has not been proved yet. Recently, the metabolic therapy, a combination of omega-3 fatty acids, coenzyme Q10 and acetyl-L-carnitine has been introduced for treating early age-related macular degeneration through improving mitochondrial dysfunction, specifically improving lipid metabolism and ATP production in the retinal pigment epithelium, improving photoreceptor turnover and reducing generation of reactive oxygen species. According to a pilot study and a randomized, placebo-controlled, double blind clinical trial, both central visual field and visual acuity slightly improved after 3-6 months of treatment and they remained unchanged by the end of the study. The difference was statistically significant as compared to the base line or to controls. These functional changes were accompanied by an improvement in fundus alterations: drusen covered area decreased significantly as compared to the base line or to control. Characteristically, all these changes were more marked in less affected eyes. A prospective case study on long-term treatment confirmed these observations. With an exception that after slight improvement, visual functions remained stable, drusen regression continued for years. Sometimes significant regression of drusen was found even in intermediate and advanced cases. All these findings strongly suggested that the metabolic therapy may be the first choice for treating age-related macular degeneration. Currently, this is the only combination of ingredients corresponding to the recommended daily allowance, and at the same time, which showed clinically proved efficacy.

PMID: 18039616 [PubMed - indexed for MEDLINE]

Ophthalmic Epidemiol. 2007 Sep-Oct;14(5):288-98.

Intake of zinc and antioxidant micronutrients and early age-related maculopathy lesions.

Morris MS, **Jacques PF**, **Chylack LT**, **Hankinson SE**, **Willett WC**, **Hubbard LD**, **Taylor A**.

Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts 02111, USA. martha.morris@tufts.edu

BACKGROUND: Macular degeneration, the end stage of age-related maculopathy (ARM), is the leading cause of legal blindness worldwide, and few modifiable risk factors are known. The high concentration of carotenoids in the macula, plus evidence linking oxidative stress to ARM and carotenoids to antioxidation, generated the hypothesis that higher antioxidant intakes can prevent ARM. Results of observational and intervention studies have been inconsistent. OBJECTIVE: To evaluate associations between intakes of zinc and antioxidant micronutrients and early ARM. METHODS: Between 1993 and 1995, ARM was assessed in 398 Boston-area women aged 53-74 y using the Wisconsin Age-related Maculopathy System of grading retinal fundus photographs. The women were a subset of the Nurses' Health Study cohort. Micronutrient intake was assessed by semi-quantitative food frequency questionnaires administered four times between 1980 and the baseline eye examinations. RESULTS: After multivariate adjustment for potential confounders, 1980 energy-adjusted intakes of alpha-carotene, beta-carotene, lycopene, total retinol, total vitamin A, and total vitamin E were significantly inversely related to the prevalence of pigmentary abnormalities (PA). Furthermore, increasing frequency of consuming foods high in alpha-or beta-carotene was associated with lower odds of PA; compared to women consuming these foods < 5 times/wk, odds ratios (95% CI) were 0.7 (0.3-1.6) for 5-6 times/wk, 0.6 (0.2-1.3) for 7-9.5 times/wk, and 0.3 (0.1-0.7)for > or =10 times/wk. Lutein/zeaxanthin intakes and more recent intakes of most carotenoids were unrelated to PA, and intakes of zinc and antioxidant micronutrients were unrelated to having large or intermediate drusen alone.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 17994438 [PubMed - indexed for MEDLINE]

Mol Biotechnol. 2007 Sep;37(1):26-30.

Carotenoids and flavonoids contribute to nutritional protection against skin damage from sunlight.

Stahl W, **Sies H**.

Institut für Biochemie und Molekularbiologie I, Heinrich-Heine-Universität Düsseldorf, Dusseldorf 40001, Germany.

The concept of photoprotection by dietary means is gaining momentum. Plant constituents such as carotenoids and flavonoids are involved in protection against excess light in plants and contribute to the prevention of UV damage in humans. As micronutrients, they are ingested with the diet and are distributed into light-exposed tissues, such as skin or the eye where they provide systemic photoprotection. beta-Carotene and lycopene prevent UV-induced erythema formation. Likewise, dietary flavanols exhibit photoprotection. After about 10-12 weeks of dietary intervention, a decrease in the sensitivity toward UV-induced erythema was observed in volunteers. Dietary micronutrients may contribute to life-long protection against harmful UV radiation.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 17914160 [PubMed - indexed for MEDLINE]

Curr Opin Ophthalmol. 2007 May;18(3):220-3.

Nutritional supplementation in age-related macular degeneration.

Coleman H, **Chew E**.

Division of Epidemiology and Clinical Research, National Eye Institute/National Institutes of Health, Bethesda, Maryland, USA.

PURPOSE OF REVIEW: This review assesses the current status of the knowledge of the role of nutrition in age-related macular degeneration - a leading cause of vision loss in the persons with European ancestry. RECENT FINDINGS: We will evaluate the different nutritional factors and both observational and interventional studies used to assess the association of nutrition with age-related macular degeneration. Persons with intermediate risk of age-related macular degeneration or advanced age-related macular degeneration in one eye are recommended to take the formulation proven in the Age-Related Eye Disease Study (AREDS) to be successful in preventing the development of advanced age-related macular degeneration by 25%. The formulation consists of vitamins C, E, beta-carotene and zinc. In addition, observational data suggest that high dietary intake of macular xanthophylls lutein and zeaxanthin are associated with a lower risk of advanced age-related macular degeneration. Similarly, long-chain polyunsaturated fatty acids derived from fish consumption are also associated with a decreased risk of advanced age-related macular degeneration. SUMMARY: Persons with intermediate age-related macular degeneration or advanced age-related macular degeneration (neovascular or central geographic atrophy) in one eye should consider taking the AREDS-type supplements. Further evaluation of nutritional factors, specifically, lutein/zeaxanthin and omega-3 fatty acids will be tested in a multicenter controlled, randomized trial - the Age-Related Eye Disease Study 2 (AREDS2).

Publication Types:

- Review

PMID: 17435429 [PubMed - indexed for MEDLINE]

Vitam Horm. 2007;75:117-30.

Conversion of beta-carotene to retinal pigment.

Biesalski HK, **Chichili GR**, **Frank J**, **von Lintig J**, **Nohr D**.

Department of Biological Chemistry and Nutrition, University of Hohenheim Stuttgart, Germany.

Vitamin A and its active metabolite retinoic acid (RA)(1) play a major role in development, differentiation, and support of various tissues and organs of numerous species. To assure the supply of target tissues with vitamin A, long-lasting stores are built in the liver from which retinol can be transported by a specific protein to the peripheral tissues to be metabolized to either RA or reesterified to form intracellular stores. Vitamin A cannot be synthesized de novo by animals and thus has to be taken up from animal food sources or as provitamin A carotenoids, the latter being converted by central cleavage of the molecule to retinal in the intestine. The recent demonstration that the responsible beta-carotene cleaving enzyme beta,beta-carotene 15,15'-monooxygenase (Bcmo1) is also present in other tissues led to numerous investigations on the molecular structure and function of this enzyme in several species, including the fruit fly, chicken, mouse, and also human. Also a second enzyme, beta,beta-carotene-9',10'-monooxygenase (Bcmo2), which cleaves beta-carotene eccentrically to apo-carotenals has been described. Retinal pigment epithelial cells were shown to contain Bcmo1 and to be able to cleave beta-carotene into retinal in vitro, offering a new pathway for vitamin A production in another tissue than the intestine, possibly explaining the more mild vitamin A deficiency symptoms of two human siblings lacking the retinol-binding protein for the transport of hepatic vitamin A to the target tissues. In addition, alternative ways to combat vitamin A deficiency of specific targets by the supplementation with beta-carotene or even molecular therapies seem to be the future.

Publication Types:

- Review

PMID: 17368314 [PubMed - indexed for MEDLINE]

Br J Nutr. 2006 Oct;96(4):643-9.

Protective effects of tomato extract with elevated beta-carotene levels on oxidative stress in ARPE-19 cells.

Chichili GR, **Nohr D**, **Frank J**, **Flaccus A**, **Fraser PD**, **Enfissi EM**, **Biesalski HK**.

Institute of Biological Chemistry and Nutrition, University of Hohenheim, Garbenstrasse 30, University of Hohenheim, D-70599 Stuttgart, Germany.

Epidemiological studies show that dietary products rich in carotenoids delay the progression of age-related macular degeneration. Experimental evidence from cellular studies on the antioxidant actions of carotenoids in the retinal pigment epithelium is still, however, fragmentary. The present study examined the uptake and protective potential of dietary carotenoids from tomato on the human retinal pigment epithelial cell line ARPE-19. ARPE-19 cells were incubated in medium supplemented with tomato extract containing high levels of beta-carotene, lycopene and traces of lutein. The cellular uptake of carotenoids was analysed by reverse-phase HPLC. Oxidative stress was induced by treatment with 1 mm-H2O2. Nitrotyrosine was detected by immunocytochemistry, and oxidised proteins (protein carbonyls) were measured by a quantitative ELISA method. Lipid peroxidation was assessed by quantifying thiobarbituric acid reactive substances. ARPE-19 cells preferentially accumulated lutein and beta-carotene rather than lycopene. Nitrotyrosine formation was considerably reduced in cells incubated with tomato extract compared with controls after H2O2 treatment. Protein carbonyls were reduced by 30 % (P = 0.015), and the formation of thiobarbituric acid-reactive substances was reduced by 140 % (P = 0.003) in cells incubated with tomato extract. The present study provides the experimental evidence for protective effects of dietary tomatoes rich in carotenoids on oxidative stress in the retinal pigment epithelium.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17010222 [PubMed - indexed for MEDLINE]

Invest Ophthalmol Vis Sci. 2005 Oct;46(10):3562-9.

beta-Carotene conversion into vitamin A in human retinal pigment epithelial cells.

Chichili GR, **Nohr D**, **Schäffer M**, **von Lintig J**, **Biesalski HK**.

Institute of Biological Chemistry and Nutrition, University of Hohenheim, Stuttgart, Germany.

PURPOSE: Vitamin A is essential for vision. The key step in the vitamin A biosynthetic pathway is the oxidative cleavage of beta-carotene into retinal by the enzyme beta,beta-carotene-15,15'-monooxygenase (BCO). The purpose of the study was to investigate beta-carotene metabolism and its effects on BCO expression in the human retinal pigment epithelial (RPE) cell line D407. METHODS: BCO mRNA and protein expression were analyzed by real-time quantitative PCR and Western blot analysis, respectively. BCO activity was assayed in protein extracts isolated from D407 cells. The conversion of beta-carotene to retinoids was determined by measuring retinol levels in D407 cells on beta-carotene supplementation. RESULTS: By RT-PCR, BCO mRNA was detected in D407 cells, bovine RPE, and retina. Western blot analyses revealed the presence of BCO at the protein level in D407 cells. Exogenous beta-carotene application to D407 cells resulted in a concentration (75% at 0.5 microM and 96% at 5 microM; $P < 0.05$)- and time (127% at 2 hours and 97% at 4 hours in 5 microM beta-carotene, $P < 0.05$)-dependent upregulation of BCO mRNA expression. Application of exogenous retinoic acid downregulated BCO mRNA levels at higher concentrations (1 microM; -96%, $P < 0.0005$) and upregulated it at a lower concentration (0.01 microM; 399%, $P < 0.005$). The RAR-a-specific antagonist upregulated BCO expression by sixfold ($P < 0.005$). Tests for enzymatic activity demonstrated that the mRNA upregulation resulted in enzymatically active BCO protein (7.3 ng all-trans-retinal/h per milligram of protein). Furthermore, D407 cells took up beta-carotene in a time-dependent manner and converted it to retinol. CONCLUSIONS: The results suggest that BCO is expressed in the RPE and that beta-carotene can be metabolized into retinol. beta-Carotene cleavage in the RPE may be an alternative pathway that would ensure the retinoid supply of photoreceptor cells.

Publication Types:

- Research Support, Non-U.S. Gov't

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J Histochem Cytochem. 2005 Nov;53(11):1403-12. Epub 2005 Jun 27.

Cell type-specific expression of beta-carotene 9',10'-monooxygenase in human tissues.

Lindqvist A, **He YG**, **Andersson S**.

University of Texas Southwestern Medical Center, Department of Obstetrics-Gynecology, F2.106 5323 Harry Hines Blvd., Dallas, TX 75390-9032, USA.

The symmetrically cleaving beta-carotene 15,15'-monooxygenase (BCO1) catalyzes the first step in the conversion of provitamin A carotenoids to vitamin A in the mucosa of the small intestine. This enzyme is also expressed in epithelia in a variety of extraintestinal tissues. The newly discovered beta-carotene 9',10'-monooxygenase (BCO2) catalyzes asymmetric cleavage of carotenoids. To gain some insight into the physiological role of BCO2, we determined the expression pattern of BCO2 mRNA and protein in human tissues. By immunohistochemical analysis it was revealed that BCO2 was detected in cell types that are known to express BCO1, such as epithelial cells in the mucosa of small intestine and stomach, parenchymal cells in liver, Leydig and Sertoli cells in testis, kidney tubules, adrenal gland, exocrine pancreas, and retinal pigment epithelium and ciliary body pigment epithelia in the eye. BCO2 was uniquely detected in cardiac and skeletal muscle cells, prostate and endometrial connective tissue, and endocrine pancreas. The finding that the BCO2 enzyme was expressed in some tissues and cell types that are not sensitive to vitamin A deficiency and where no BCO1 has been detected suggests that BCO2 may also be involved in biological processes other than vitamin A synthesis.

Publication Types:

- Comparative Study
- Research Support, N.I.H., Extramural

PMID: 15983114 [PubMed - indexed for MEDLINE]

Eur J Neurosci. 2005 Jan;21(1):59-68.

Photoreceptor morphology is severely affected in the beta,beta-carotene-15,15'-oxygenase (bcox) zebrafish morphant.

Biehlmaier O, **Lampert JM**, **von Lintig J**, **Kohler K**.

Experimental Ophthalmology, University Eye Hospital, Roentgenweg 11, 72076 Tuebingen, Germany. konrad.kohler@uni-tuebingen.de

The retinoic acid molecule, a vitamin A derivative, is of key importance for eye and photoreceptor development in vertebrates. Several studies have provided evidence that the ventral part of the retina is particularly susceptible to impairment in retinoid signalling during the period of its development. In zebrafish, targeted gene knockdown of beta,beta-carotene-15,15'-oxygenase (bcox), the key enzyme for vitamin A formation, provokes a loss of retinoid signalling during early eye development that results in microphthalmia at larval stages. Using this model, we analysed the consequences of this for the retinal morphology of the fish larvae in structural details. Our analyses revealed that rods and cones do not express photoreceptor specific proteins (rhodopsin, peanut agglutinin, zpr1) in the peripheral retina. The photoreceptors in the central retina showed shortened outer segments, and electron dense debris in their intermembranal space. The number of phagosomes was increased, and cell death was frequently observed in the outer nuclear layer. Furthermore, the number of Muller cells was significantly reduced in the inner nuclear layer. Thus, we found that the lack of retinoid signalling strongly effects photoreceptor development in the ventral and dorsal retina. In addition, shortened outer segments and cell death of the remaining photoreceptors in the central retina indicate that there is an ongoing need for retinoid signalling for photoreceptor integrity and survival at later developmental stages.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 15654843 [PubMed - indexed for MEDLINE]

Am J Epidemiol. 2003 Aug 15;158(4):337-46.

Antioxidant intake and primary open-angle glaucoma: a prospective study.

Kang JH, **Pasquale LR**, **Willett W**, **Rosner B**, **Egan KM**, **Faberowski N**, **Hankinson SE**.

Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115, USA. nhjhk@channing.harvard.edu

The relation between dietary antioxidant intake and primary open-angle glaucoma risk was examined in participants aged over 40 years in the Nurses' Health Study (n = 76,200) and the Health Professionals Follow-up Study (n = 40,284). They were followed biennially from 1980 and 1986, respectively, to 1996, during periods when they received an eye examination. Dietary intakes were measured repeatedly from 1980 in the Nurses' Health Study and from 1986 in the Health Professionals Follow-up Study using validated food frequency questionnaires. The authors analyzed 474 self-reported glaucoma cases confirmed by medical chart review to have primary open-angle glaucoma with visual field loss. The authors used Cox proportional hazards models for cohort-specific multivariate analyses, and results were pooled using random effects models. The pooled multivariate rate ratios for primary open-angle glaucoma comparing the highest versus lowest quintile of cumulative updated intake were 1.17 (95% confidence interval (CI): 0.87, 1.58) for alpha-carotene, 1.10 (95% CI: 0.82, 1.48) for beta-carotene, 0.95 (95% CI: 0.70, 1.29) for beta-cryptoxanthin, 0.82 (95% CI: 0.60, 1.12) for lycopene, 0.92 (95% CI: 0.69, 1.24) for lutein/zeaxanthin, 1.05 (95% CI: 0.59, 1.89) for vitamin C, 0.97 (95% CI: 0.62, 1.52) for vitamin E, and 1.11 (95% CI: 0.82, 1.51) for vitamin A. In conclusion, the authors did not observe any strong associations between antioxidant consumption and the risk of primary open-angle glaucoma.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.
- Research Support, U.S. Gov't, P.H.S.

PMID: 12915499 [PubMed - indexed for MEDLINE]

Ophthalmologe. 2003 Mar;100(3):181-9.

- **[Antioxidant micronutrients and cataract.Review and comparison of the AREDS and REACT cataract studies]**
  [Article in German]

  Schalch W, **Chylack LT**.

  Roche Vitamins AG, Basel, Switzerland. wolfgang.schalch@roche.com

  Age-related cataract remains the major cause of preventable blindness throughout the world. It has long been realized that one of the important etiological factors for this disease is oxidative and in particular photooxidative damage to the lens.Therefore, the antioxidant micronutrients, vitamins C and E and the carotenoids, in particular beta-carotene, have been discussed as factors that could reduce the risk for this disease. The present article reviews what is known about the transport of these substances to the lens, their accumulation, and their concentrations in the lens. Furthermore, the available epidemiological literature is briefly mentioned, but more emphasis has been placed on a description and discussion of major clinical intervention studies. Finally, the design and results of two of those trials using antioxidant micronutrients, the Age-Related Eye Disease Study (AREDS) and the Roche European American Cataract Trial (REACT), are compared.The AREDS trial did show a positive effect only for age-related macular degeneration but not for cataract, while the REACT trial demonstrated a small but statistically significant deceleration of cataract progression.The techniques for following the course of a cataract in the REACT study were more sensitive to subtle changes than those used in the AREDS study, and this may have been one important factor accounting for the differences.The authors' detailed comparison of these studies, however, suggests that even more important may have been the fact that in the REACT study intervention started earlier in the disease process,with higher doses of vitamins C and E and beta-carotene and consequently with larger plasma concentrations of these antioxidant micronutrients.The REACT trial results support the early complementation of a diversified diet with supplements containing vitamins C and E and beta-carotene as well as other carotenoids.The authors also believe that it is reasonable to include these micronutrients in the therapeutic armamentarium of general ophthalmological practice.

  PMID: 12640546 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2002 Mar;75(3):540-9.

- **Long-term intake of vitamins and carotenoids and odds of early age-related cortical and posterior subcapsular lens opacities.**

Taylor A, **Jacques PF**, **Chylack LT Jr**, **Hankinson SE**, **Khu PM**, **Rogers G**, **Friend J**, **Tung W**, **Wolfe JK**, **Padhye N**, **Willett WC**.

Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111, USA. ataylor@hnrc.tufs.edu

BACKGROUND: Proper nutrition appears to protect against cataracts. Few studies have related nutrition to the odds of developing cortical or posterior subcapsular (PSC) cataracts. OBJECTIVE: We assessed the relation between usual nutrient intakes and age-related cortical and PSC lens opacities. DESIGN: We studied 492 nondiabetic women aged 53-73 y from the Nurses' Health Study cohort who were without previously diagnosed cataracts. Usual nutrient intake was calculated as the average intake from 5 food-frequency questionnaires collected over a 13-15-y period before the eye examination. Duration of vitamin supplement use was determined from 7 questionnaires collected during this same period. We defined cortical opacities as grade > or = 0.5 and subcapsular opacities as grade > or =0.3 of the Lens Opacities Classification System III. RESULTS: Some lenses had more than one opacity. No nutrient measure was related to prevalence of opacities in the full sample, but significant interactions were seen between age and vitamin C intake (P = 0.02) for odds of cortical opacities and between smoking status and folate (P = 0.02), alpha-carotene (P = 0.02), beta-carotene (P = 0.005), and total carotenoids (P = 0.02) for odds of PSC opacities. For women aged <60 y, a vitamin C intake > or = 362 mg/d was associated with a 57% lower odds ratio (0.43; 95% CI: 0.2, 0.93) of developing a cortical cataract than was an intake <140 mg/d, and use of vitamin C supplements for > or = 10 y was associated with a 60% lower odds ratio (0.40; 0.18, 0.87) than was no vitamin C supplement use. Prevalence of PSC opacities was related to total carotenoid intake in women who never smoked (P = 0.02). CONCLUSIONS: Our results support a role for vitamin C in diminishing the risk of cortical cataracts in women aged <60 y and for carotenoids in diminishing the risk of PSC cataracts in women who have never smoked.

PMID: 11864861 [PubMed - indexed for MEDLINE]

Zeaxanthin and Eye Health

Clin Dermatol. 2009 Mar-Apr;27(2):195-201.

Lutein and zeaxanthin in eye and skin health.

Roberts RL, **Green J**, **Lewis B**.

Kemin Health, LC, 600 E Court Avenue, Suite A, Des Moines, IA 50309-2058, USA. richard.roberts@kemin.com

Less than 20 of the hundreds of carotenoids found in nature are found in the human body. These carotenoids are present in the body from the foods or dietary supplements that humans consume. The body does not synthesize them. Among the carotenoids present in the body, only lutein and its coexistent isomer, zeaxanthin, are found in that portion of the eye where light is focused by the lens, namely, the macula lutea. Numerous studies have shown that lutein and zeaxanthin may provide significant protection against the potential damage caused by light striking this portion of the retina. In the eye, lutein and zeaxanthin have been shown to filter high-energy wavelengths of visible light and act as antioxidants to protect against the formation of reactive oxygen species and subsequent free radicals. Human studies have demonstrated that lutein and zeaxanthin are present in the skin, and animal studies have provided evidence of significant efficacy against light-induced skin damage, especially the ultraviolet wavelengths. Little was known about the protective effects of these carotenoids in human skin until recently. This article reviews the scientific literature pertaining to the effects that lutein and zeaxanthin exhibit in the human eye and skin.

Publication Types:

- Review

PMID: 19168000 [PubMed - indexed for MEDLINE]

Curr Eye Res. 2009 Apr;34(4):311-8.

Zeaxanthin, a retinal carotenoid, protects retinal cells against oxidative stress.

Nakajima Y, **Shimazawa M**, **Otsubo K**, **Ishibashi T**, **Hara H**.

Department of Biofunctional Evaluation, Molecular Pharmacology, Gifu Pharmaceutical University, Gifu, Japan.

PURPOSE: To investigate whether zeaxanthin, the predominant carotenoid pigment of the macular pigments in human retina, provides neuroprotection against retinal cell damage. METHODS: We used in vitro cultured retinal ganglion cells (RGCs), specifically RGC-5, an E1A virus-transformed rat cell line. Cell damage was induced either by a 24-hr exposure to hydrogen peroxide (H2O2) or by serum deprivation. Cell viability was measured using the tetrazolium salt, WST-8. The scavenging capacity of zeaxanthin for H2O2, superoxide anion radical (O2.-), and hydroxyl radical (HO.) was measured using a radical scavenging capacity assay with CM-H2DCFDA, a reactive oxygen species (ROS)-sensitive probe. RESULTS: When added to RGC-5 cell cultures, 0.1, 10, and 1 microM zeaxanthin scavenged the free radicals induced by H2O2, O2.-, and HO., respectively. In addition, pretreatment with 1 microM zeaxanthin permitted scavenging of staurosporine-induced intracellular radicals. Zeaxanthin also inhibited the neurotoxicity induced by H2O2 or serum deprivation and scavenged the intracellular radicals induced by H2O2 or serum deprivation. CONCLUSIONS: Our results suggest that zeaxanthin provides effective protection against oxidative stress-induced retinal cell damage.

PMID: 19373580 [PubMed - in process

J Ocul Biol Dis Infor. 2008 Mar;1(1):12-18.

Macular and serum carotenoid concentrations in patients with malabsorption syndromes.

Ward MS, **Zhao DY**, **Bernstein PS**.

Department of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah School of Medicine, 65 Mario Capecchi Drive, Salt Lake City, Utah 84132, USA.

The carotenoids lutein and zeaxanthin are believed to protect the human macula by absorbing blue light and quenching free radicals. Intestinal malabsorption syndromes such as celiac and Crohn's disease are known to cause deficiencies of lipid-soluble nutrients. We hypothesized that subjects with nutrient malabsorption syndromes will demonstrate lower carotenoid levels in the macula and blood, and that these lower levels may correlate with early-onset maculopathy. Resonance Raman spectrographic (RRS) measurements of macular carotenoid levels were collected from subjects with and without a history of malabsorption syndromes. Carotenoids were extracted from serum and analyzed by high performance liquid chromatography (HPLC). Subjects with malabsorption (n=22) had 37% lower levels of macular carotenoids on average versus controls (n=25, P<0.001). Malabsorption was not associated with decreased serum carotenoid levels. Convincing signs of early maculopathy were not observed. We conclude that intestinal malabsorption results in lower macular carotenoid levels.

PMID: 19081745 [PubMed]

PMCID: PMC2600549

Ophthalmic Epidemiol. 2008 Nov-Dec;15(6):389-401.

Carotenoids and co-antioxidants in age-related maculopathy: design and methods.

Neelam K, Hogg RE, Stevenson MR, Johnston E, Anderson R, Beatty S, Chakravarthy U.

Waterford Institute of Technology, Waterford, Republic of Ireland.

Age-related macular degeneration (AMD), is the leading cause of blind registration in the Western World among individuals 65 years or older. Early AMD, a clinical state without overt functional loss, is said to be present clinically when yellowish deposits known as drusen and/or alterations of fundus pigmentation are seen in the macular retina. Although the etiopathogenesis of AMD remains uncertain, there is a growing body of evidence in support of the view that cumulative oxidative damage plays a causal role. Appropriate dietary antioxidant supplementation is likely to be beneficial in maintaining visual function in patients with AMD, and preventing or delaying the progression of early AMD to late AMD. The Carotenoids in Age-Related Maculopathy (CARMA) Study is a randomized and double-masked clinical trial of antioxidant supplementation versus placebo in 433 participants with either early AMD features of sufficient severity in at least one eye or any level of AMD in one eye with late AMD (neovascular AMD or central geographic atrophy) in the fellow eye. The aim of the CARMA Study is to investigate whether lutein and zeaxanthin, in combination with co-antioxidants (vitamin C, E, and zinc), has a beneficial effect on visual function and/or prevention of progression from early to late stages of disease. The primary outcome is improved or preserved distance visual acuity at 12 months. Secondary outcomes include improved or preserved interferometric acuity, contrast sensitivity, shape discrimination ability, and change in AMD severity as monitored by fundus photography. This article outlines the CARMA Study design and methodology, including its rationale.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't
- Review

PMID: 19065432 [PubMed - indexed for MEDLINE]

Nutr Rev. 2008 Dec;66(12):695-702.

Possible role for dietary lutein and zeaxanthin in visual development.

Hammond BR Jr.

Vision Sciences Laboratory, University of Georgia, Athens, Georgia 30602, USA.

The possibility that the macular carotenoids, lutein (L), and zeaxanthin (Z), could retard age-related changes in the eye and prevent the eye diseases that result from such changes (namely, cataract and macular degeneration) has been carefully studied. A role for the carotenoids very early in life, however, has received far less attention. Nevertheless, an influence on visual development is likely. Retinal L and Z, for instance, would influence the development of the visual system if they 1) altered input during a critical/sensitive period of visual development and/or 2) influenced maturation and/or 3) protected the retina during a period when it was particularly vulnerable. The available evidence indicates that the pigments may play a role in all three of these areas.

Publication Types:

- Review

PMID: 19019038 [PubMed - indexed for MEDLINE]

Arch Ophthalmol. 2008 Oct;126(10):1396-403.

Sunlight exposure, antioxidants, and age-related macular degeneration.

Fletcher AE, **Bentham GC**, **Agnew M**, **Young IS**, **Augood C**, **Chakravarthy U**, **de Jong PT**, **Rahu M**, **Seland J**, **Soubrane G**, **Tomazzoli L**, **Topouzis F**, **Vingerling JR**, **Vioque J**.

Department of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, Keppel Street, London, England.
astrid.fletcher@lshtm.ac.uk

OBJECTIVE: To examine the association of sunlight exposure and antioxidant level with age-related macular degeneration (AMD). METHODS: Four thousand seven hundred fifty-three participants aged 65 years or older in the European Eye Study underwent fundus photography, were interviewed for adult lifetime sunlight exposure, and gave blood for antioxidant analysis. Blue light exposure was estimated by combining meteorologic and questionnaire data. RESULTS: Data on sunlight exposure and antioxidants were available in 101 individuals with neovascular AMD, 2182 with early AMD, and 2117 controls. No association was found between blue light exposure and neovascular or early AMD. Significant associations were found between blue light exposure and neovascular AMD in individuals in the quartile of lowest antioxidant level-vitamin C, zeaxanthin, vitamin E, and dietary zinc-with an odds ratio of about 1.4 for 1 standard deviation unit increase in blue light exposure. Higher odds ratios for blue light were observed with combined low antioxidant levels, especially vitamin C, zeaxanthin, and vitamin E (odds ratio, 3.7; 95% confidence interval, 1.6-8.9), which were also associated with early stages of AMD. CONCLUSIONS: Although it is not possible to establish causality between sunlight exposure and neovascular AMD, our results suggest that people in the general population should use ocular protection and follow dietary recommendations for the key antioxidant nutrients.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18852418 [PubMed - indexed for MEDLINE]

Med Monatsschr Pharm. 2008 Aug;31(8):299-308.

[Lutein and eye health--current state of discussion]

[Article in German]

Hahn A, **Mang B**.

Leibniz Universität Hannover, Institut für Lebensmittelwissenschaft, Hannover.
andreas.hahn@lw.uni-hannover.de

Due to increased life expectancy the number of people with age-related diseases like age-related macular degeneration (AMD) will grow. Currently AMD is incurable and only a few therapeutic strategies are available. Therefore prevention becomes more important. Protective effects related to eye health are discussed for the two carotenoids lutein and zeaxanthin. Meanwhile both substances are offered as food supplements to a great extent. Both carotenoids lutein and zeaxanthin are accumulated in the retina, especially in the macula lutea. They are able to absorb blue light, which damages photoreceptors and pigmentary epithelium. Due to their antioxidative properties they can reduce changes in membrane permeability via quenching reactive oxygen species and free radicals. Research studies suppose lutein and zeaxanthin may contribute to improvement of vision in patients with AMD and other eye diseases. Based on the scientific rationale, these carotenoids may be effective in the prevention of age-related eye diseases. However, this issue has to be examined in a differentiated way.

Publication Types:

- English Abstract
- Review

PMID: 18754570 [PubMed - indexed for MEDLINE]

Vopr Pitan. 2008;77(3):34-8.

[Light-absorbing and antiradical properties of a product with lutein and zeaxanthin in vitro and kinetics of carotinoids at single oral administration on rats]

[Article in Russian]

Karlina MV, **Pozharitskaia ON**, **Kosman VM**, **Shikov AN**, **Makarov VG**.

Light-absorbing and antiradical properties of the new product on a basis of lutein and zeaxanthin for correction of eye diseases in model system of initiated oxidation of isopropylbenzene were investigated. It is shown, that the product is the effective light-absorbing agent and inhibitor of free-radical oxidation in vitro. In experiments on animals (rat) the pharmacokinetics of the product was investigated at single oral administration. A simple, specific and sensitive RP-HPLC method for the determination of lutein in rat plasma was developed, which was applied to pharmacokinetic investigation in rats after oral administration of lutein at dose 20 mg/kg. It was established, that the peak plasma levels was achieved to 2 hour and the mean elimination half life was 2,4 hours.

Publication Types:

- English Abstract

PMID: 18669329 [PubMed - indexed for MEDLINE]

Nutr Rev. 2008 Aug;66(8):465-72.

Phytochemicals and age-related eye diseases.

Rhone M, **Basu A**.

Department of Nutritional Sciences, Oklahoma State University, Stillwater, Oklahoma 74078-6141, USA.

Cataracts, glaucoma, and age-related macular degeneration (AMD) are common causes of blindness in the elderly population of the United States. Additional risk factors include obesity, smoking, and inadequate antioxidant status. Phytochemicals, as antioxidants and anti-inflammatory agents, may help prevent or delay the progression of these eye diseases. Observational and clinical trials support the safety of higher intakes of the phytochemicals lutein and zeaxanthin and their association with reducing risks of cataracts in healthy postmenopausal women and improving clinical features of AMD in patients. Additional phytochemicals of emerging interest, like green tea catechins, anthocyanins, resveratrol, and Ginkgo biloba, shown to ameliorate ocular oxidative stress, deserve more attention in future clinical trials.

Publication Types:

- Review

PMID: 18667008 [PubMed - indexed for MEDLINE]

Exp Eye Res. 2001 Mar;72(3):215-23.

Identification and quantitation of carotenoids and their metabolites in the tissues of the human eye.

Bernstein PS, **Khachik F**, **Carvalho LS**, **Muir GJ**, **Zhao DY**, **Katz NB**.

Department of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT 84132, USA. paul.bernstein@hsc.utah.edu

There is increasing evidence that the macular pigment carotenoids, lutein and zeaxanthin, may play an important role in the prevention of age-related macular degeneration, cataract, and other blinding disorders. Although it is well known that the retina and lens are enriched in these carotenoids, relatively little is known about carotenoid levels in the uveal tract and in other ocular tissues. Also, the oxidative metabolism and physiological functions of the ocular carotenoids are not fully understood. Thus, we have set out to identify and quantify the complete spectrum of dietary carotenoids and their oxidative metabolites in a systematic manner in all tissues of the human eye in order to gain better insight into their ocular physiology.Human donor eyes were dissected, and carotenoid extracts from ocular tissues [retinal pigment epithelium/choroid (RPE/choroid), macula, peripheral retina, ciliary body, iris, lens, vitreous, cornea, and sclera] were analysed by high-performance liquid chromatography (HPLC). Carotenoids were identified and quantified by comparing their chromatographic and spectral profiles with those of authentic standards.Nearly all ocular structures examined with the exception of vitreous, cornea, and sclera had quantifiable levels of dietary (3R,3'R,6'R)-lutein, zeaxanthin, their geometrical (E / Z) isomers, as well as their metabolites, (3R,3'S,6'R)-lutein (3'-epilutein) and 3-hydroxy-beta,epsilon-caroten-3'-one. In addition, human ciliary body revealed the presence of monohydroxycarotenoids and hydrocarbon carotenoids, while only the latter group was detected in human RPE/choroid. Uveal structures (iris, ciliary body, and RPE/choroid) account for approximately 50% of the eye's total carotenoids and approximately 30% of the lutein and zeaxanthin. In the iris, these pigments are likely to play a role in filtering out phototoxic short-wavelength visible light, while they are more likely to act as antioxidants in the ciliary body. Both mechanisms, light screening and antioxidant, may be operative in the RPE/choroid in addition to a possible function of this tissue in the transport of dihydroxycarotenoids from the circulating blood to the retina. This report lends further support for the critical role of lutein, zeaxanthin, and other ocular carotenoids in protecting the eye from light-induced oxidative damage and aging.

PMID: 11180970 [PubMed - indexed for MEDLINE]

Invest Ophthalmol Vis Sci. 2000 Apr;41(5):1200-9.

Lutein and zeaxanthin concentrations in rod outer segment membranes from perifoveal and peripheral human retina.

Rapp LM, **Maple SS**, **Choi JH**.
Cullen Eye Institute, Department of Ophthalmology, Baylor College of Medicine, Houston, Texas 77030, USA. lrapp@bcm.tmc.edu

PURPOSE: In addition to acting as an optical filter, macular (carotenoid) pigment has been hypothesized to function as an antioxidant in the human retina by inhibiting the peroxidation of long-chain polyunsaturated fatty acids. However, at its location of highest density in the inner (prereceptoral) layers of the foveal retina, a specific requirement for antioxidant protection would not be predicted. The purpose of this study was to determine whether lutein and zeaxanthin, the major carotenoids comprising the macular pigment, are present in rod outer segment (ROS) membranes where the concentration of long-chain polyunsaturated fatty acids, and susceptibility to oxidation, is highest. METHODS: Retinas from human donor eyes were dissected to obtain two regions: an annular ring of 1.5- to 4-mm eccentricity representing the area centralis excluding the fovea (perifoveal retina) and the remaining retina outside this region (peripheral retina). ROS and residual (ROS-depleted) retinal membranes were isolated from these regions by differential centrifugation and their purity checked by polyacrylamide gel electrophoresis and fatty acid analysis. Lutein and zeaxanthin were analyzed by high-performance liquid chromatography and their concentrations expressed relative to membrane protein. Preparation of membranes and analysis of carotenoids were performed in parallel on bovine retinas for comparison to a nonprimate species. Carotenoid concentrations were also determined for retinal pigment epithelium harvested from human eyes. RESULTS: ROS membranes prepared from perifoveal and peripheral regions of human retina were found to be of high purity as indicated by the presence of a dense opsin band on protein gels. Fatty acid analysis of human ROS membranes showed a characteristic enrichment of docosahexaenoic acid relative to residual membranes. Membranes prepared from bovine retinas had protein profiles and fatty acid composition similar to those from human retinas. Carotenoid analysis showed that lutein and zeaxanthin were present in ROS and residual human retinal membranes. The combined concentration of lutein plus zeaxanthin was 70% higher in human ROS than in residual membranes. Lutein plus zeaxanthin in human ROS membranes was 2.7 times more concentrated in the perifoveal than the peripheral retinal region. Lutein and zeaxanthin were consistently detected in human retinal pigment epithelium at relatively low concentrations. CONCLUSIONS: The presence of lutein and zeaxanthin in human ROS membranes raises the possibility that they function as antioxidants in this cell compartment. The finding of a higher concentration of these carotenoids in ROS of the perifoveal retina lends support to their proposed protective role in age-related macular degeneration.

PMID: 10752961 [PubMed - indexed for MEDLINE]

Exp Eye Res. 2000 Sep;71(3):239-45.

Lutein and zeaxanthin in the eyes, serum and diet of human subjects.

Bone RA, **Landrum JT**, **Dixon Z**, **Chen Y**, **Llerena CM**.

Department of Physics, Florida International University, Miami, FL 33199, USA.

Inverse associations have been reported between the incidence of advanced, neovascular, age-related macular degeneration (AMD) and the combined lutein (L) and zeaxanthin (Z) intake in the diet, and L and Z concentration in the blood serum. We suggest that persons with high levels of L and Z in either the diet or serum would probably have, in addition, relatively high densities of these carotenoids in the macula, the so-called 'macular pigment'. Several lines of evidence point to a potential protective effect by the macular pigment against AMD. In this study we examined the relationship between dietary intake of L and Z using a food frequency questionnaire; concentration of L and Z in the serum, determined by high-performance liquid chromatography, and macular pigment optical density, obtained by flicker photometry. Nineteen subjects participated. We also analysed the serum and retinas, as autopsy samples, from 23 tissue donors in order to obtain the concentration of L and Z in these tissues. The results reveal positive, though weak, associations between dietary intake of L and Z and serum concentration of L and Z, and between serum concentration of L and Z and macular pigment density. We estimate that approximately half of the variability in the subjects' serum concentration of L and Z can be explained by their dietary intake of L and Z, and about one third of the variability in their macular pigment density can be attributed to their serum concentration of L and Z. These results, together with the reported associations between risk of AMD and dietary and serum L and Z, support the hypothesis that low concentrations of macular pigment may be associated with an increased risk of AMD.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, P.H.S.

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Invest Ophthalmol Vis Sci. 1997 Aug;38(9):1802-11.

Identification of lutein and zeaxanthin oxidation products in human and monkey retinas.

Khachik F, **Bernstein PS**, **Garland DL**.

Beltsville Human Nutrition Research Center, Carotenoids Research Unit, US Department of Agriculture, Beltsville, Maryland 20705, USA.

PURPOSE: To characterize fully all the major and minor carotenoids and their metabolites in human retina and probe for the presence of the oxidative metabolites of lutein and zeaxanthin. METHODS: Carotenoids of a composite of 58 pairs of human retinas and a monkey retina were elucidated by comparing their high-performance liquid chromatography (HPLC)-ultraviolet/visible absorption spectrophotometry (UV/Vis)-mass spectrometry (MS) profile with those of authentic standards prepared by organic synthesis. RESULTS: In addition to lutein and zeaxanthin, several oxidation products of these compounds were present in the extracts from human retina. A major carotenoid resulting from direct oxidation of lutein was identified as 3-hydroxy-beta, epsilon-caroten-3'-one. Minor carotenoids were identified as: 3'-epilutein, epsilon,epsilon-carotene-3,3'-diol, epsilon,epsilon-carotene-3,3'-dione, 3'-hydroxy-epsilon,epsilon-caroten-3-one, and 2,6-cyclolycopene-1,5-diol. Several of the geometric isomers of lutein and zeaxanthin were also detected at low concentrations. These were as follows: 9-cis-lutein, 9'-cislutein, 13-cis-lutein, 13'-cis-lutein, 9-cis-zeaxanthin, and 13-cis-zeaxanthin. Similar results were also obtained from HPLC analysis of a freshly dissected monkey retina. CONCLUSIONS: Lutein, zeaxanthin, 3'-epilutein, and 3-hydroxy-beta,epsilon-caroten-3'-one in human retina may be interconverted through a series of oxidation-reduction reactions similar to our earlier proposed metabolic transformation of these compounds in humans. The presence of the direct oxidation product of lutein and 3'-epilutein (metabolite of lutein and zeaxanthin) in human retina suggests that lutein and zeaxanthin may act as antioxidants to protect the macula against short-wavelength visible light. The proposed oxidative-reductive pathways for lutein and zeaxanthin in human retina, may therefore play an important role in prevention of age-related macular degeneration and cataracts.

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Invest Ophthalmol Vis Sci. 1997 Aug;38(9):1795-801.

Dietary modification of human macular pigment density.

Hammond BR Jr, **Johnson EJ**, **Russell RM**, **Krinsky NI**, **Yeum KJ**, **Edwards RB**, **Snodderly DM**.

Department of Social and Behavioral Sciences, College of Arts and Sciences, Arizona State University West, Phoenix 85069-7100, USA.

PURPOSE: The retinal carotenoids lutein (L) and zeaxanthin (Z) that form the macular pigment (MP) may help to prevent neovascular age-related macular degeneration. The purpose of this study was to determine whether MP density in the retina could be raised by increasing dietary intake of L and Z from foods. METHODS: Macular pigment was measured psychophysically for 13 subjects. Serum concentrations of L, Z, and beta-carotene were measured by high-performance liquid chromatography. Eleven subjects modified their usual daily diets by adding 60 g of spinach (10.8 mg L, 0.3 mg Z, 5 mg beta-carotene) and ten also added 150 g of corn (0.3 mg Z, 0.4 mg L); two other subjects were given only corn. Dietary modification lasted up to 15 weeks. RESULTS: For the subjects fed spinach or spinach and corn, three types of responses to dietary modification were identified: Eight "retinal responders" had increases in serum L (mean, 33%; SD, 22%) and in MP density (mean, 19%; SD, 11%); two "retinal nonresponders" showed substantial increases in serum L (mean, 31%) but not in MP density (mean, -11%); one "serum and retinal nonresponder" showed no changes in serum L, Z, or beta-carotene and no change in MP density. For the two subjects given only corn, serum L changed little (+11%, -6%), but in one subject serum Z increased (70%) and MP density increased (25%). CONCLUSIONS: Increases in MP density were obtained within 4 weeks of dietary modification for most, but not all, subjects. When MP density increased with dietary modification, it remained elevated for at least several months after resuming an unmodified diet. Augmentation of MP for both experimental and clinical investigation appears to be feasible for many persons.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.
- Research Support, U.S. Gov't, P.H.S.

PMID: 9286268 [PubMed - indexed for MEDLINE]

Optom Vis Sci. 1997 Jul;74(7):499-504.

Density of the human crystalline lens is related to the macular pigment carotenoids, lutein and zeaxanthin.

Hammond BR Jr, Wooten BR, Snodderly DM.

Vision Sciences Laboratory, College of Arts & Sciences, Arizona State University, Phoenix, USA. BHammond@asuvm.inre.asu.edu

PURPOSE: Although oxidative stress may play an important role in the development of age-related cataract, the degree of protection reported for antioxidant vitamins and carotenoids has been inconsistent across studies. These varied results may be due in part to the lack of good biomarkers for measuring the long-term nutritional status of the eye. The present experiments investigated the relationship between retinal carotenoids (i.e., macular pigment), used as a long-term measure of tissue carotenoids, and lens optical density, used as an indicator of lens health. METHODS: Macular pigment (460 nm) and lens (440, 500, and 550 nm) optical density were measured psychophysically in the same individuals. Groups of younger subjects--7 females (ages 24 to 36 years), and 5 males (ages 24 to 31 years)--were compared with older subjects--23 older females (ages 55 to 78 years), and 16 older males (ages 48 to 82 years). RESULTS: Lens density (440 nm) increased as a function of age ($r = 0.65$, $p < 0.001$), as expected. For the oldest group, a significant inverse relationship ($y = 1.53-0.83x$, $r = -0.47$, $p < 0.001$) was found between macular pigment density (440 nm) and lens density (440 nm). No relationship was found for the youngest group ($p < 0.42$). CONCLUSIONS: The main finding of this study was an age-dependent, inverse relationship between macular pigment density and lens density. Macular pigment is composed of lutein and zeaxanthin, the only two carotenoids that have been identified in the human lens. Thus, an inverse relationship between these two variables suggests that lutein and zeaxanthin, or other dietary factors with which they are correlated, may retard age-related increases in lens density.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, P.H.S.

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Am J Clin Nutr. 1995 Dec;62(6 Suppl):1448S-1461S.

Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins.

Snodderly DM.

Schepens Eye Research Institute, Macular Disease Research Center, Boston, MA 02114, USA.

Epidemiologic data indicate that individuals with low plasma concentrations of carotenoids and antioxidant vitamins and those who smoke cigarettes are at increased risk for age-related macular degeneration (AMD). Laboratory data show that carotenoids and antioxidant vitamins help to protect the retina from oxidative damage initiated in part by absorption of light. Primate retinas accumulate two carotenoids, lutein and zeaxanthin, as the macular pigment, which is most dense at the center of the fovea and declines rapidly in more peripheral regions. The retina also distributes alpha-tocopherol (vitamin E) in a nonuniform spatial pattern. The region of monkey retinas where carotenoids and vitamin E are both low corresponds with a locus where early signs of AMD often appear in humans. The combination of evidence suggests that carotenoids and antioxidant vitamins may help to retard some of the destructive processes in the retina and the retinal pigment epithelium that lead to age-related degeneration of the macula.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, P.H.S.
- Review

PMID: 7495246 [PubMed - indexed for MEDLINE]

JAMA. 1994 Nov 9;272(18):1413-20.

Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group.

Seddon JM, **Ajani UA**, **Sperduto RD**, **Hiller R**, **Blair N**, **Burton TC**, **Farber MD**, **Gragoudas ES**, **Haller J**, **Miller DT**, **et al**.

Epidemiology Unit, Massachusetts Eye and Ear Infirmary, Boston 02114.

OBJECTIVE--To evaluate the relationships between dietary intake of carotenoids and vitamins A, C, and E and the risk of neovascular age-related macular degeneration (AMD), the leading cause of irreversible blindness among adults. DESIGN--The multicenter Eye Disease Case-Control Study. SETTING--Five ophthalmology centers in the United States. PATIENTS--A total of 356 case subjects who were diagnosed with the advanced stage of AMD within 1 year prior to their enrollment, aged 55 to 80 years, and residing near a participating clinical center. The 520 control subjects were from the same geographic areas as case subjects, had other ocular diseases, and were frequency-matched to cases according to age and sex. MAIN OUTCOME MEASURES--The relative risk for AMD was estimated according to dietary indicators of antioxidant status, controlling for smoking and other risk factors, by using multiple logistic-regression analyses. RESULTS--A higher dietary intake of carotenoids was associated with a lower risk for AMD. Adjusting for other risk factors for AMD, we found that those in the highest quintile of carotenoid intake had a 43% lower risk for AMD compared with those in the lowest quintile (odds ratio, 0.57; 95% confidence interval, 0.35 to 0.92; P for trend = .02). Among the specific carotenoids, lutein and zeaxanthin, which are primarily obtained from dark green, leafy vegetables, were most strongly associated with a reduced risk for AMD (P for trend = .001). Several food items rich in carotenoids were inversely associated with AMD. In particular, a higher frequency of intake of spinach or collard greens was associated with a substantially lower risk for AMD (P for trend < .001). The intake of preformed vitamin A (retinol) was not appreciably related to AMD. Neither vitamin E nor total vitamin C consumption was associated with a statistically significant reduced risk for AMD, although a possibly lower risk for AMD was suggested among those with higher intake of vitamin C, particularly from foods. CONCLUSION--Increasing the consumption of foods rich in certain carotenoids, in particular dark green, leafy vegetables, may decrease the risk of developing advanced or exudative AMD, the most visually disabling form of macular degeneration among older people. These findings support the need for further studies of this relationship.

Publication Types:

- Multicenter Study
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, P.H.S.

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Anticancer Res. 2005 Nov-Dec;25(6B):3871-6.

The photoreceptor protector zeaxanthin induces cell death in neuroblastoma cells.

Maccarrone M, **Bari M**, **Gasperi V**, **Demmig-Adams B**.

Department of Biomedical Sciences, University of Teramo, Piazza A. Moro 45, 64100 Teramo, Italy. mmaccarrone@unite.it

BACKGROUND: The dietary carotenoid zeaxanthin protects against age-related eye disease by preventing apoptosis in photoreceptor cells. This study examined the effect of zeaxanthin on neuroblastoma cells in which apoptosis can be induced with lipid peroxidation products. Since zeaxanthin can inhibit lipid peroxidation and beta-carotene inhibits lipoxygenase (LOX) activity, it was of concern that zeaxanthin might inhibit apoptosis in these cancer cells. MATERIALS AND METHODS: Apoptosis-resistant CHP100 neuroblastoma cells were treated with zeaxanthin. Apoptosis was assessed via an immunoassay for histone-associated DNA fragments and cytofluorimetric analysis of apoptotic body formation. The effect of zeaxanthin on the activity of two model LOXs and LOX-mediated lipid peroxidation in liposomes was assessed. RESULTS: Zeaxanthin strongly induced apoptosis in neuroblastoma cells. Consistent with this finding, zeaxanthin did not inhibit LOX activity. CONCLUSION: Zeaxanthin is a remarkable dietary factor that is able to induce apoptosis in neuroblastoma cells while being able to prevent apoptosis in healthy cells.

PMID: 16309173 [PubMed - indexed for MEDLINE]

Invest Ophthalmol Vis Sci. 2002 Nov;43(11):3538-49.

Elevated retinal zeaxanthin and prevention of light-induced photoreceptor cell death in quail.

Thomson LR, **Toyoda Y**, **Langner A**, **Delori FC**, **Garnett KM**, **Craft N**, **Nichols CR**, **Cheng KM**, **Dorey CK**.

Schepens Eye Research Institute, Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts, USA.

PURPOSE: Inferential evidence indicates that macular pigments (lutein and zeaxanthin) protect photoreceptors and/or retard age-related macular degeneration. These experiments tested the hypothesis that retinal zeaxanthin prevents light-induced photoreceptor cell death. METHODS: Retinal damage was assessed in quail fed a carotenoid-deficient (C-) diet for 6 months. Groups of 16 birds (8 male, 8 female) were fed a C- diet supplemented with 35 mg 3R,3'R-zeaxanthin for 1, 3, or 7 days; one group was continued on C- diets. Half of each group was exposed to intermittent 3200-lux white light (10 1-hour intervals separated by 2 hours in dark). After 14 additional hours in the dark, one retina of each quail was collected for HPLC analysis, and the contralateral retina was embedded in paraffin for counts of apoptotic nuclei. RESULTS: After 7 days' supplementation, concentrations of zeaxanthin in serum, liver, and fat had increased by factors of 50.8, 43.2, and 6.5, respectively (all $P < 0.001$). In contrast, retinal zeaxanthin fluctuated significantly upward on day 3, but there was no net change on day 7. The number of apoptotic rods and cones in light-damaged eyes correlated significantly and inversely with zeaxanthin concentration in the contralateral retina ($r = -0.61$; $P < 0.0001$ and $r = -0.54$; $P < 0.002$), but not with serum zeaxanthin. Similar correlations were observed with retinal lutein, which correlated strongly with retinal zeaxanthin ($r = 0.95$; $P < 0.0001$). CONCLUSIONS: Retinal zeaxanthin dose dependently reduced light-induced photoreceptor apoptosis; elevated serum levels did not. These data provide the first experimental evidence that xanthophyll carotenoids protect photoreceptors in vivo.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 12407166 [PubMed - indexed for MEDLINE]

Zeaxanthin and Brain Health

Appl Microbiol Biotechnol. 2007 Apr;74(6):1350-7. Epub 2007 Jan 11.

Rare carotenoids, (3R)-saproxanthin and (3R,2'S)-myxol, isolated from novel marine bacteria (Flavobacteriaceae) and their antioxidative activities.

Shindo K, **Kikuta K**, **Suzuki A**, **Katsuta A**, **Kasai H**, **Yasumoto-Hirose M**, **Matsuo Y**, **Misawa N**, **Takaichi S**.

Department of Food and Nutrition, Japan Women's University, 2-8-1 Mejirodai, Tokyo 112-8681, Japan. Kshindo@fc.jwu.ac.jp

We isolated three orange or yellow pigment-producing marine bacteria, strains 04OKA-13-27 (MBIC08261), 04OKA-17-12 (MBIC08260), and YM6-073 (MBIC06409), off the coast of Okinawa Prefecture in Japan. These strains were classified as novel species of the family Flavobacteriaceae based on their 16S rRNA gene sequence. They were cultured, and the major carotenoids produced were purified by chromatographic methods. Their structures were determined by spectral data to be (3R)-saproxanthin (strain 04OKA-13-27), (3R,2'S)-myxol (strain YM6-073), and (3R,3'R)-zeaxanthin (strains YM6-073 and 04OKA-17-12). Saproxanthin and myxol, which are monocyclic carotenoids rarely found in nature, demonstrated significant antioxidative activities against lipid peroxidation in the rat brain homogenate model and a neuro-protective effect from L-glutamate toxicity.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17216447 [PubMed - indexed for MEDLINE]

J Nutr Health Aging. 2004;8(3):156-62.

Carotenoid, tocopherol, and retinol concentrations in elderly human brain.

Craft NE, **Haitema TB**, **Garnett KM**, **Fitch KA**, **Dorey CK**.

Craft Technologies, Inc., 4344 Frank Price Church Road, Wilson, NC 27893, USA. ncraft@crafttechnologies.com

BACKGROUND: Antioxidants, such as tocopherols and carotenoids, have been implicated in the prevention of degenerative diseases. Although correlations have been made between diseases and tissue levels of antioxidants, to date there are no reports of individual carotenoid concentrations in human brain. OBJECTIVE: To measure the major carotenoids, tocopherols, and retinol in frontal and occipital regions of human brain. DESIGN: Ten samples of brain tissue from frontal lobe cortex and occipital cortex of five cadavers were examined. Sections were dissected into gray and white matter, extracted with organic solvents, and analyzed by HPLC. RESULTS: At least 16 carotenoids, 3 tocopherols, and retinol were present in human brain. Major carotenoids were identified as lutein, zeaxanthin, anhydrolutein, alpha- cryptoxanthin, beta- cryptoxanthin, alpha-carotene, cis- and trans-betacarotene, and cis- and trans-lycopene. Xanthophylls (oxygenated carotenoids) accounted for 66-77% of total carotenoids in all brain regions examined. Similar to neural retina, the ratio of zeaxanthin to lutein was high and these two xanthophylls were significantly correlated ($p < 0.0001$). The tocopherol isomers occurred in the brain over a wider range of mean concentrations (0.11-17.9 nmol/g) than either retinol (87.8 - 163.3 pmol/g) or the identified carotenoids (1.8-23.0 pmol/g). CONCLUSIONS: The frontal cortex, generally vulnerable in Alzheimer's disease, had higher concentrations of all analytes than the occipital cortex which is generally unaffected. Moreover, frontal lobes, but not occipital lobes, exhibited an age-related decline in retinol, total tocopherols, total xanthophylls and total carotenoids. The importance of these differences and the role(s) of these antioxidants in the brain remain to be determined.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15129301 [PubMed - indexed for MEDLINE]

Free Radic Res. 2002 Mar;36(3):265-8.

Plasma carotenoid and malondialdehyde levels in ischemic stroke patients: relationship to early outcome.

Polidori MC, **Cherubini A**, **Stahl W**, **Senin U**, **Sies H**, **Mecocci P**.

Institute of Physiological Chemistry I, Heinrich-Heine University, Düsseldorf, Germany. polidori@uni-duesseldorf.de

An association between ischemic stroke and increased oxidative stress has been suggested from animal studies. However, there is a lack of evidence with respect to this association in humans. Here, the time course of plasma levels of six carotenoids, which are lipophilic micronutrients with antioxidant properties, as well as of malondialdehyde (MDA), a marker of lipid peroxidation, was followed in ischemic stroke patients. Plasma levels of lutein, zeaxanthin, beta-cryptoxanthin, lycopene, alpha- and beta-carotene, as well as MDA were measured by high-performance liquid chromatography in 28 subjects (19 men and nine women aged 76.9+/-8.7 years) with an acute ischemic stroke of recent onset (<24h) on admission, after 6 and 24 h, and on days 3, 5, and 7. Carotenoid and MDA levels in patients on admission were compared with those of age- and sex-matched controls. Plasma levels of lutein, lycopene, alpha- and beta-carotene were significantly lower and levels of MDA were significantly higher in patients in comparison with controls. Significantly higher levels of MDA and lower levels of lutein were found in patients with a poor early-outcome (functional decline) after ischemic stroke as compared to patients who remained functionally stable. These findings suggest that the majority of plasma carotenoids are lowered immediately after an ischemic stroke, perhaps as a result of increased oxidative stress, as indicated by a concomitant rise in MDA concentrations. Among the carotenoids, only lutein plasma changes are associated with a poor early-outcome.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 12071344 [PubMed - indexed for MEDLINE]

Zeaxanthin as a Hepatoprotective

Dig Dis Sci. 2009 May 8. [Epub ahead of print]

Protective Effects of the Carotenoid Zeaxanthin in Experimental Nonalcoholic Steatohepatitis.

Chamberlain SM, **Hall JD**, **Patel J**, **Lee JR**, **Marcus DM**, **Sridhar S**, **Romero MJ**, **Labazi M**, **Caldwell RW**, **Bartoli M**.

Section of Gastroenterology, Department of Medicine, Medical College of Georgia, BBR-2538, Augusta, GA, 30912, USA, schamberlain@mcg.edu.

Fat infiltration and inflammation cause liver injury and fibrosis and may progress to nonalcoholic steatohepatitis (NASH) and end-stage liver disease. Currently, there are no effective treatments for NASH. Zeaxanthin is a carotenoid which has been shown to be preferentially accumulated in the adipose tissue and liver. We hypothesized that treatment with zeaxanthin may decrease oxidative stress in the liver and, possibly, halt the inflammation and fibrosis associated with NASH. Here we tested zeaxanthin effects in preventing progression of liver injury in a model of NASH. Mongolian gerbils, fed a methionine-choline-deficient diet, were treated with different doses of zeaxanthin. We assessed histopathological changes by hematoxylin-eosin and Masson trichrome staining and determined oxidative stress by measuring lipid peroxidation. The obtained results show that zeaxanthin significantly prevented NASH progression by decreasing oxidative stress and liver fibrosis, thus suggesting a potential therapeutic application for this carotenoid in the management of NASH.

PMID: 19424798 [PubMed - as supplied by publisher]

Res Commun Mol Pathol Pharmacol. 1997 Sep;97(3):301-14.

Zeaxanthin dipalmitate from Lycium chinense has hepatoprotective activity.

Kim HP, **Kim SY**, **Lee EJ**, **Kim YC**, **Kim YC**.

College of Pharmacy, Seoul National University, Korea.

We previously reported the isolation of zeaxanthin and zeaxanthin dipalmitate using bioactivity-guided fractionation to discover hepatoprotective components of Lycium chinense against carbon tetrachloride induced hepatotoxicity. The present study was designed to uncover the effects of zeaxanthin dipalmitate on hepatic parenchymal and nonparenchymal cells in vitro. Uptake of [3H]thymidine by cultured rat Ito cells in response to zeaxanthin dipalmitate was measured. Collagen synthesis was assessed by the collagenase digestion method. The effects of zeaxanthin dipalmitate on the formation of nitric oxide (NO) and the release of tumor necrosis factor-alpha (TNF-alpha) from Kupffer cells and peritoneal macrophages were also assayed. Zeaxanthin dipalmitate showed a significant hepatoprotective activity against carbon tetrachloride toxicity. Cellular malondialdehyde (MDA) levels declined significantly with the treatment of the compound in a concentration dependent manner. Zeaxanthin dipalmitate significantly inhibited the uptake of [3H]thymidine by Ito cells. Zeaxanthin dipalmitate also reduced collagen synthesis in Ito cells by 65.1% ($p < 0.05$) as compared to untreated controls. The formation of NO in either Kupffer cells or in peritoneal macrophages was significantly decreased by zeaxanthin dipalmitate in a concentration dependent manner. The release of TNF-alpha was somewhat less affected by the compound. From these results, we conclude that zeaxanthin dipalmitate exerts a potent hepatoprotective activity by inhibiting Ito cell proliferation, collagen synthesis and by inhibiting certain biochemical functions of Kupffer cells.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 9387190 [PubMed - indexed for MEDLINE]

Cancer Lett. 2000 Apr 3;151(1):111-5.

Inhibitory effects of carotenoids on the invasion of rat ascites hepatoma cells in culture.

Kozuki Y, **Miura Y**, **Yagasaki K**.

Department of Applied Biological Science, Tokyo Noko University, Fuchu, Japan.

The effects of carotenoids--alpha-carotene, beta-carotene, lycopene, beta-cryptoxanthin, zeaxanthin, lutein, canthaxanthin, astaxanthin--on the invasion of rat ascites hepatoma AH109A cells were investigated by co-culturing the hepatoma cells with rat mesentery-derived mesothelial cells (M-cells). All the carotenoids examined inhibited AH109A invasion in a dose-dependent manner up to 5 microM. Cancer cells previously cultured with hypoxanthine (HX) and xanthine oxidase (XO) showed a highly invasive activity. Carotenoids, 5 microM of beta-carotene and astaxanthin, suppressed this reactive oxygen species-potentiated invasive capacity by simultaneously treating AH109A cells with the carotenoids, HX and XO. These results suggest that the antioxidative property of these carotenoids may be involved in their anti-invasive action.

Publication Types:

- Research Support, Non-U.S. Gov't

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Aliment Pharmacol Ther. 2000 Mar;14(3):353-8.

Plasma antioxidant levels in chronic cholestatic liver diseases.

Floreani A, **Baragiotta A**, **Martines D**, **Naccarato R**, **D'odorico A**.
Department of Surgical and Gastroenterological Sciences, University of Padova, Italy.
aflor@ux1.unipd.it

BACKGROUND: [corrected] A predictable consequence of cholestasis is malabsorption of fat-soluble factors, (vitamins A, D, E, K) and other free radical scavengers, such as carotenoids. It has been suggested that oxygen-derived free radicals may be involved in the pathogenesis of chronic liver damage. AIMS: (i) To evaluate retinol, alpha-tocopherol and carotenoid plasma levels in two groups of patients with chronic cholestatic liver disease (primary biliary cirrhosis and primary sclerosing cholangitis); (ii) to compare the respective plasma levels with those of the general population; (iii) to correlate the plasma levels with disease severity. METHODS: A total of 105 patients with chronic cholestasis were included in the study: 86 with primary biliary cirrhosis (81 female, five male, mean age 55.5 +/- 11 years), 19 with primary sclerosing cholangitis (seven female, 12 male, mean age 35 +/- 11 years; six patients had associated inflammatory bowel disease); 105 sex- and age-matched subjects from the general population in the same geographical area (88 female, 17 male, mean age 51.3.5 +/- 10 years) served as controls. Carotenoids (lutein zeaxanthin, lycopene, beta-carotene, alpha-carotene, beta-cryptoxanthin), retinol and alpha-tocopherol were assayed by high-pressure liquid chromatography. A food frequency questionnaire was administered to each subject to evaluate the quality and the quantity of dietary compounds. Data were processed by analysis of variance and linear regression analysis, as appropriate. RESULTS: Both primary biliary cirrhosis and primary sclerosing cholangitis patients had significantly lower levels of retinol, alpha-tocopherol, total carotenoids, lutein, zeaxanthin, lycopene, alpha- and beta-carotene than controls ($P < 0.0001$). Among the cholestatic patients, no significant difference in the concentration of antioxidants was observed between primary biliary cirrhosis and primary sclerosing cholangitis subjects. Anti-oxidant plasma levels were not affected by the severity of the histological stage in primary biliary cirrhosis, but a negative correlation was found between total carotenoids and both alkaline phosphatase (ALP) and gammaglutamyl transpeptidase (GGT) ($P < 0.013$ and $P < 0.018$, respectively). Within the primary sclerosing cholangitis group, no correlation was found between total carotenoids and cholestatic enzymes. Nutritional intake in cholestatic patients was comparable to controls, including fruit and vegetable intake. CONCLUSIONS: Although no clinical sign of deficiency is evident, plasma levels of antioxidants are low in cholestatic patients even in early stages of the disease. This is probably due to malabsorption of fat-soluble vitamins, as well as other mechanisms of hepatic release, suggesting the need for dietary supplementation.

Publication Types:

- Clinical Trial
- Research Support, Non-U.S. Gov't

PMID: 10735930 [PubMed - indexed for MEDLINE]

Zeaxanthin as a Hepatoprotective

J Hepatol. 1995 Nov;23(5):550-6.

Carotenoids and tocopherols in various hepatobiliary conditions.

Leo MA, Ahmed S, Aleynik SI, Siegel JH, Kasmin F, Lieber CS.
Section of Liver Disease and Nutrition, Alcohol Research Center, Bronx, NY 10468, USA.

BACKGROUND: Previous studies revealed hepatic interactions of beta-carotene with alcohol in non-human primates, but bile carotenoids and alpha-tocopherol have not previously been explored in man. METHODS: To compare the plasma and biliary concentrations of carotenoids, retinoids and tocopherols among controls and patients with biliary and pancreatic diseases, these compounds were measured by high performance liquid chromatography in bile collected during 41 endoscopic retrograde cholangiopancreatographies. RESULTS: In 14 subjects with normal endoscopic retrograde cholangiopancreatography (controls), bile contained beta-carotene, alpha-carotene, lycopene, cryptoxanthin, lutein+zeaxanthin (23.9 +/- 6.6, 3.9 +/- 1.1, 39.9 +/- 21.6, 22.5 +/- 4.6, 217.1 +/- 27.8 nmol/l, respectively) with corresponding plasma values of 399.7 +/- 72.6, 88.5 +/- 18.8, 588.2 +/- 75.0, 145.1 +/- 25.9, 319.3 +/- 33.7 nmol/l. In 13 patients in whom bile duct stones impaired biliary excretion (as reflected by raised serum bilirubin), beta-carotene was significantly decreased in both plasma (199.6 +/- 35.5 nmol/l) and bile (9.4 +/- 2.0 nmol/l), with a similar trend for other carotenoids. The beta-carotene plasma/bile ratio was maintained, as well as a correlation between the two ($r = 0.56$; $p = 0.048$). Furthermore, in three subjects with complete biliary obstruction, plasma beta-carotene (35.8 +/- 20.2 nmol/l) decreased even more, probably reflecting malabsorption. In 11 patients with pancreatic diseases, plasma and bile beta-carotene were 107.9 +/- 17.8 and 6.6 +/- 2.0 nmol/l respectively, while a correlation between the two ($r = 0.70$; $p = 0.018$) again persisted, confirming the role of plasma beta-carotene in determining bile concentrations. Indeed, for the entire group ($n = 41$), the correlation between plasma and bile or red blood cell beta-carotene was highly significant, whereas plasma/red blood cell ratios remained unchanged. Similar findings were observed for alpha-tocopherol, with 8.4 +/- 0.9 mumol/l in control bile (vs. 23.2 +/- 1.7 mumol/l in plasma), and no significant change in the various groups. CONCLUSIONS: 1) Carotenoids and tocopherols undergo biliary excretion in man. 2) Biliary concentrations reflect plasma levels in both normal and pathologic states. 3) Decreased biliary excretion of carotenoids does not increase plasma concentrations.

PMID: 8583143 [PubMed - indexed for MEDLINE]

Zeaxanthin as a Hepatoprotective

Iron and Immunity

Arzneimittelforschung. 2007;57(6A):417-25.

Effect of oral supplementation with iron(III)-hydroxide polymaltose complex on the immunological profile of adolescents with varying iron status.

Devaki PB, **Chandra RK**, **Geisser P**.

Department of Home Science, S.V University, Tirupati, India.
pbabydevaki@yahoo.co.in

OBJECTIVE: To assess the effects of iron supplementation on immunological parameters of adolescents with varying iron status. METHOD: Adolescents of both sexes with varying iron status were allocated to four treatment groups by using inclusion criteria. Three of the four groups received iron(III)-hydroxide polymaltose complex (IPC, Maltofer) containing 100 mg of iron 6 days a week for 8 months. The fourth group was given a placebo. Immunological parameters were assessed at baseline and after 4 and 8 months of supplementation. RESULTS: Increases from baseline to 4 months and from 4 to 8 months of supplementation were observed for Bactericidal Capacity of Neutrophils (BCA), NitroBlue Tetrazolium Reduction Test (NBT), and phytohaemagglutinin (PHA) in all three supplemented groups. No increase was found in the control placebo group except for PHA. No side effects were noted in any participants. CONCLUSION: IPC supplementation for eight months led to significant improvements of immunological parameters in iron deficient adolescents with and without anemia.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17691591 [PubMed - indexed for MEDLINE]

Biol Trace Elem Res. 2009 Feb;127(2):95-101. Epub 2008 Sep 30.

Early effects on T lymphocyte response to iron deficiency in mice. Short communication.

Saldanha-Araujo F, **Souza AM**.

Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirao Preto, São Paolo, Brazil.

Iron deficiency is a common nutritional disorder, affecting about 30% of the world population. Deficits in iron functional compartments have suppressive effects on the immune system. Environmental problems, age, and other nutrient deficiencies are some of the situations which make human studies difficult and warrant the use of animal models. This study aimed to investigate alterations in the immune system by inducing iron deficiency and promoting recuperation in a mouse model. Hemoglobin concentration, hematocrit, liver iron store, and flow cytometry analyses of cell-surface transferrin receptor (CD71) on peripheral blood and spleen CD4+ and CD8+ T lymphocyte were performed in the control (C) and the iron-deficient (ID) groups of animals at the beginning and end of the experiment. Hematological indices of C and ID mice were not different but the iron stores of ID mice were significantly reduced. Although T cell subsets were not altered, the percentage of T cells expressing CD71 was significantly increased by ID. The results suggest that iron deficiency induced by our experimental model would mimic the early events in the onset of anemia, where thymus atrophy is not enough to influence subset composition of T cells, which can still respond to iron deficiency by upregulating the expression of transferrin receptor.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18825318 [PubMed - indexed for MEDLINE]

J Autoimmun. 2008 Feb-Mar;30(1-2):84-9.

New functions for an iron storage protein: the role of ferritin in immunity and autoimmunity.

Recalcati S, **Invernizzi P**, **Arosio P**, **Cairo G**.

Institute of General Pathology, University of Milan, Via Mangiagalli 31, 20133 Milan, Italy. stefania.recalcati@unimi.it

Ferritin is a ubiquitous and specialised protein involved in the intracellular storage of iron; it is also present in serum and other biological fluids, although its secretion processes are still unclear. We here review evidence supporting the hypothesis that macrophages play a role in the production and secretion of extracellular ferritin, as well as evidence supporting a novel function as a signalling molecule and immune regulator. In particular, H-ferritin, which inhibits the proliferation of lymphoid and myeloid cells, may be regarded as a negative regulator of human and murine hematopoiesis. The idea that it also acts as a signalling protein has been supported by the cloning and characterisation of the specific H-ferritin receptor TIM-2, a member of the TIM gene family. A number of studies of the mouse TIM gene family indicate that this protein plays an important role in immune-mediated diseases. This last finding, together with the fact that ferritin acts as an immuno-suppressor, has allowed us to formulate hypotheses regarding the possible role of alterations of H-ferritin/TIM-2 binding/signalling in the pathogenesis of autoimmune diseases.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18191543 [PubMed - indexed for MEDLINE]

Br J Nutr. 2007 Oct;98 Suppl 1:S24-8.

Iron, copper and immunocompetence.

Muñoz C, **Rios E**, **Olivos J**, **Brunser O**, **Olivares M**.

INTA, University of Chile, Santiago, Chile. cmunoz@inta.cl

Microminerals including copper and iron are essential to immunity and health in human beings. The development of powerful tools in analytical cell biology and molecular genetics has facilitated efforts to identify specific cellular and molecular functions of trace elements in the maturation, activation and functions of host defence mechanisms. Selected recent reports about the role of copper and iron nutrition on immune functions are critically analysed here. Effects of trace element supplementation on infectious morbidity are also reviewed. While micromineral deficiencies, in general, may have widespread effects on nearly all components of immune response, these effects can be reversed by supplementation. However, the conflicting effects of iron deficiency and iron supplementation in vitro on the defensive systems reveals the urgent need for further additional information on the in vivo situation. In the elderly, vaccination against respiratory infections is likely to protect only 30-70% of the population. However, it may be possible to modulate immune function and ultimately reduce the severity of infections through micronutrient supplementation. Thus, microminerals contribute to the maintenance of the balance between immunity and health in humans.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 17922954 [PubMed - indexed for MEDLINE]

Free Radic Biol Med. 2008 Feb 1;44(3):483-92. Epub 2007 Oct 22.

Ceruloplasmin expression by human peripheral blood lymphocytes: a new link between immunity and iron metabolism.

Banha J, **Marques L**, **Oliveira R**, **Martins Mde F**, **Paixão E**, **Pereira D**, **Malhó R**, **Penque D**, **Costa L**.

Instituto Nacional de Saúde Dr. Ricardo Jorge, IP (INSA), Lisboa, Portugal.

Ceruloplasmin (CP) is a multicopper oxidase involved in the acute phase reaction to stress. Although the physiological role of CP is uncertain, its role in iron (Fe) homeostasis and protection against free radical-initiated cell injury has been widely documented. Previous studies showed the existence of two molecular isoforms of CP: secreted CP (sCP) and a membrane glycosylphosphatidylinositol (GPI)-anchored form of CP (GPI-CP). sCP is produced mainly by the liver and is abundant in human serum whereas GPI-CP is expressed in mammalian astrocytes, rat leptomeningeal cells, and Sertolli cells. Herein, we show using RT-PCR that human peripheral blood lymphocytes (huPBL) constitutively express the transcripts for both CP molecular isoforms previously reported. Also, expression of CP in huPBL is demonstrated by immunofluorescence with confocal microscopy and flow cytometry analysis using cells isolated from healthy blood donors with normal Fe status. Importantly, the results obtained show that natural killer cells have a significantly higher CP expression compared to all other major lymphocyte subsets. In this context, the involvement of lymphocyte-derived CP on host defense processes via its anti/prooxidant properties is proposed, giving further support for a close functional interaction between the immune system and the Fe metabolism.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17991445 [PubMed - indexed for MEDLINE]

Pediatr Res. 2007 May;61(5 Pt 1):520-4.

Maternal stress during pregnancy predisposes for iron deficiency in infant monkeys impacting innate immunity.

Coe CL, **Lubach GR**, **Shirtcliff EA**.

Harlow Center for Biological Psychology, University of Wisconsin, Madison, Wisconsin 53715, USA. ccoe@wisc.edu

The influence of maternal stress during pregnancy on the postpartum iron status and immune maturation of infants was investigated in a nonhuman primate model. Forty infant rhesus monkeys were generated from two types of disturbed pregnancies, early or late gestation stress, and compared with 24 undisturbed controls. Prenatal stress increased the prevalence and magnitude of iron deficiency (ID) as the infants' growth-related demands for iron exceeded dietary intake from breast milk. At 4-6 mo of age, the emergence of ID significantly accentuated an effect of prenatal stress on natural killer cell activity, an important component of innate immunity. These findings indicate that maternal stress, especially early in pregnancy, should be added to the list of risk factors that warrant closer scrutiny of hematological profiles in fast-growing babies.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 17413860 [PubMed - indexed for MEDLINE]

Indian J Med Res. 2006 Dec;124(6):647-54.

Impact of iron deficiency anaemia on T lymphocytes & their subsets in children.

Mullick S, **Rusia U**, **Sikka M**, **Faridi MA**.

Department of Pathology, St John's Medical College, Bangalore, India.

BACKGROUND & OBJECTIVES: While there is evidence of an altered immune profile in iron deficiency, the precise immunoregulatory role of iron is not known. Information particular in children who are vulnerable to iron deficiency and infection, is lacking. We undertook this study with the aim of documenting the changes in T cell subsets in children in the age group of 1 to 5 yr with iron deficiency. METHODS: The levels of T lymphocytes, their CD4+ and CD8+ subsets and the CD4 : CD8 ratio were evaluated in 40 iron deficient and 30 healthy children. The impact of oral iron supplementation for three months on the same parameters was also noted in 30 children. RESULTS: Significantly lower levels of T lymphocytes as well as CD4+ cells was observed in the iron deficient children ($P<0.01$ and 0.002 respectively). The CD4 : CD8 ratio was also significantly lower in this group ($P<0.05$). Iron supplementation improved the CD4 counts significantly. INTERPRETATION & CONCLUSION: Our study demonstrated quantitatively altered T cell subsets in iron deficiency in children, and a relationship between the severity of haematological and immunological compromise. The clinical and epidemiological implications of this relationship have topical relevance since ID is the most common micronutrient deficiency worldwide.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17287552 [PubMed - indexed for MEDLINE]

Immunobiology. 2006;211(4):295-314. Epub 2006 Apr 17.

Iron-withholding strategy in innate immunity.

Ong ST, **Ho JZ**, **Ho B**, **Ding JL**.

Department of Biological Sciences, National University of Singapore, 14 Science Drive 4, Singapore 117543.

The knowledge of how organisms fight infections has largely been built upon the ability of host innate immune molecules to recognize microbial determinants. Although of overwhelming importance, pathogen recognition is but only one of the facets of innate immunity. A primitive yet effective antimicrobial mechanism which operates by depriving microbial organisms of their nutrients has been brought into the forefront of innate immunity once again. Such a tactic is commonly referred to as the iron-withholding strategy of innate immunity. In this review, we introduce various vertebrate iron-binding proteins and their invertebrate homologues, so as to impress upon readers an obscured arm of innate immune defense. An excellent comprehension of the mechanics of innate immunity paves the way for the possibility that novel antimicrobial therapeutics may emerge one day to overcome the prevalent antibiotic resistance in bacteria.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 16697921 [PubMed - indexed for MEDLINE]

Wei Sheng Yan Jiu. 2006 Jan;35(1):79-81.

[Effects of iron deficiency anemia on immunity and infectious disease in pregnant women]

[Article in Chinese]

Tang YM, **Chen XZ**, **Li GR**, **Zhou RH**, **Ning H**, **Yan H**.

North China Coal Medical College, Tangshan 063000, China.

OBJECTIVE: To review the changes in immune function and incidence of infectious diseases in pregnant women with iron deficiency anemia (IDA), especially marginalde-ficiency of iron. METHODS: T lymphocyte subsets level (CD3+, CD4+ and CD8+), nature kill cells activity (CD16), interleukin-2 (IL-2) and serum IgA, IgG, IgM and complement C3 were determined in 3 different wormen groups, including 69 IDA pregnant women who were diagnosed by Hemoglobin, concentrations of free erythocyte porphrin and serum ferritin from 280 pregnant women during 30-38weeka of gestation, 52 random sampling normal pregnant women and 50 no pregnant women examined before marriage. RESULTS: The prevalenoe of IDA for pregnant women is 24.6%. The average concentration of Hb for pregnant women of IDA is 102.00(6.00 g/L The level of CD3+ and CD4+ cells, the ratio of CD4+/CD8+ cells, serum IL-2 as well as IgG levels in the pregnant women were significantly lower than that of those normal pregnant women ($P < 0.01$, $P < 0.05$, $P < 0.05$, $P < 0.01$). With the decreasing extent of Hb, these significant immunological indices of pregnant women will degrease. The incidence of infectious diseases in IDA pregnant women was significantly higher than that in normal pregnant women ($P < 0.05$). CONCLUSION: There are significantly effects of IDA on cellular immune function and infectious disease during pregnancy. The study on effects of IDA during pregnancy on nature kill cells activity (CD16) and incidence of infectious diseases during puerperium should be continued by increasing sample's number.

Publication Types:

- English Abstract

PMID: 16598942 [PubMed - in process]

Exp Mol Med. 2005 Aug 31;37(4):297-310.

Iron chelator induces MIP-alpha/CCL20 in human intestinal epithelial cells: implication for triggering mucosal adaptive immunity.

Lee HJ, **Choi SC**, **Choi EY**, **Lee MH**, **Seo GS**, **Kim EC**, **Yang BJ**, **Lee MS**, **Shin YI**, **Park KI**, **Jun CD**.

Department of Physiology, Kyungpook National University School of Medicine, Daegu 700-422, Korea.

A previous report by this laboratory demonstrated that bacterial iron chelator (siderophore) triggers inflammatory signals, including the production of CXC chemokine IL-8, in human intestinal epithelial cells (IECs). Microarray-based gene expression profiling revealed that iron chelator also induces macrophage inflammatory protein 3 alpha (MIP-3alpha)/CC chemokine-ligand 20 (CCL20). As CCL20 is chemotactic for the cells involved in host adaptive immunity, this suggests that iron chelator may stimulate IECs to have the capacity to link mucosal innate and adaptive immunity. The basal medium from iron chelator deferoxamine (DFO)-treated HT-29 monolayers was as chemotactic as recombinant human CCL20 at equivalent concentrations to attract CCR6(+) cells. The increase of CCL20 protein secretion appeared to correspond to that of CCL20 mRNA levels, as determined by real-time quantitative RT-PCR. The efficacy of DFO at inducing CCL20 mRNA was also observed in human PBMCs and in THP-1 cells, but not in human umbilical vein endothelial cells. Interestingly, unlike other proinflammatory cytokines, such as TNF-alpha and IL-1beta, a time-dependent experiment revealed that DFO slowly induces CCL20, suggesting a novel mechanism of action. A pharmacologic study also revealed that multiple signaling pathways are differentially involved in CCL20 production by DFO, while some of those pathways are not involved in TNF-alpha-induced CCL20 production. Collectively, these results demonstrate that, in addition to some bacterial products known to induce host adaptive immune responses, direct chelation of host iron by infected bacteria may also contribute to the initiation of host adaptive immunity in the intestinal mucosa.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16155407 [PubMed - indexed for MEDLINE]

Int J Biochem Cell Biol. 2005 Sep;37(9):1768-73. Epub 2005 Mar 16.

Hepcidin: a direct link between iron metabolism and immunity.

Vyoral D, **Petrák J**.

Institute of Hematology and Blood Transfusion, Prague, Czech Republic. vyoral@uhkt.cz

Hepcidin, originally discovered in urine as a bactericidal peptide synthesized by hepatocytes was later proved to be a key regulator of iron metabolism at the whole body level, namely, in conditions of altered iron demand such as the increased or decreased total amount of body iron, inflammation, hypoxia and anemia. The major mechanism of hepcidin function seems to be the regulation of transmembrane iron transport. Hepcidin binds to its receptor, protein ferroportin, which serves as a transmembrane iron channel enabling iron efflux from cells. The hepcidin-ferroportin complex is then degraded in lysosomes and iron is locked inside the cells (mainly enterocytes, hepatocytes and macrophages). This leads to lowering of iron absorption in the intestine and to a decrease in serum iron concentration. Utilizing this mechanism, hepcidin regulates serum iron levels during inflammation, infection and possibly also in cancer. Under these conditions iron is shifted from circulation into cellular stores in hepatocytes and macrophages, making it less available for invading microorganisms and tumor cells. In anemia and hypoxia, hepcidin regulates the availability of iron for erythropoiesis. Hepcidin or hepcidin-related therapeutics could find a place in the treatment of various diseases such as hemochromatosis and anemia of chronic disease.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 16009323 [PubMed - indexed for MEDLINE]

Biomed Pharmacother. 2005 Jul;59(6):307-11.

Phagocytic capacity and apoptosis of peripheral blood cells from patients with iron deficiency anemia.

Bergman M, **Salman H**, **Pinchasi R**, **Straussberg R**, **Djaldetti M**, **Bessler H**.

Department of Medicine C, Rabin Medical Center, Golda Campus, Petah Tiqva, Israel.

Following clinical observations that patients with iron deficiency anemia (IDA) are more susceptible to infections than non-anemic individuals, the phagocytic capacity and number of apoptotic peripheral white blood cells (PWBC) from patients with IDA were examined. PWBC from 15 patients with IDA and from 18 healthy donors were incubated with various doses of iron. Phagocytosis was examined using latex particles and apoptosis was evaluated by a flow cytometric assay using propidium iodide staining. The percentage of phagocyting polymorphonuclear cells was lower in IDA patients compared to that of the controls. However, there was no difference in the percentage of phagocyting monocytes from individuals of both groups. The number of latex beads engulfed by each polymorphonuclear or monocyte was lower in IDA patients. Incubation with 100 microg% of iron did not affect the phagocytic ability of both cell types in IDA patients, but increased that of control cells. Incubation with 300 microg% of iron caused an increase in the phagocytic capacity of patients' cells and a decrease in that function in cells from controls. Higher dose (500 microg%) induced suppression of phagocytosis in cells from both groups. There was no difference in the number of apoptotic cells from individuals of both groups. Apoptosis of polymorphonuclears, but not mononuclear cells from both controls and IDA patients showed a linear dependency on the iron concentration in the medium. It is possible that the impaired phagocytic capacity of the PBWC found in patients with IDA contribute to the increased susceptibility to infections observed in these individuals.

PMID: 15996848 [PubMed - indexed for MEDLINE]

Hematol J. 2005;5(7):579-83.

The effect of iron deficiency anemia on the function of the immune system.

Ekiz C, **Agaoglu L**, **Karakas Z**, **Gurel N**, **Yalcin I**.

Division of Hematology/Oncology, Department of Pediatrics, Istanbul School of Medicine, Istanbul University, Istanbul, Turkey.

We aimed to study the effect of iron deficiency anemia (IDA) on immunity. In 32 children with IDA and 29 normal children, the percentage of T-lymphocyte subgroups, the level of serum interleukin-6 (IL-6); and the phagocytic activity, the oxidative burst activity of neutrophils and monocytes and the levels of immunoglobulins were compared. There was no difference in the distribution of T-lymphocyte subgroups. The mean IL-6 levels was 5.6+/-3.9 pg/ml in children with IDA and 10.3+/-5.3 pg/ml in the control group (P<0.001). The percentage of neutrophils with oxidative burst activity when stimulated with pma was 53.4+/-32.7% in children with IDA and 81.7+/-14.3% in the control group (P=0.005). The percentage of monocytes with oxidative burst activity was 13.8+/-11.7% in children with IDA and 35+/-20.0% in the control group (P<0.001) when stimulated with pma. and 4.3+/-3.1 versus 9.7+/-6.0% (P=0.008) when stimulated with fMLP. The ratio of neutrophils with phagocytic activity was 58.6+/-23.3% in the anemic group; and 74.2+/-17.7% in the control group (P=0.057). The ratio of monocytes with phagocytic activity was 24.3+/-12.0% in the anemic group; and 42.9+/-13.4% in the control group (P=0.001). IgG4 level was 16.7+/-16.6 mg/dl in children with IDA and 51.8+/-40.7 mg/dl in healthy children (P<0.05). These results suggest that humoral, cell-mediated and nonspecific immunity and the activity of cytokines which have an important role in various steps of immunogenic mechanisms are influenced by iron deficiency anemia.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 15692603 [PubMed - indexed for MEDLINE]

Zhonghua Xue Ye Xue Za Zhi. 1997 Nov;18(11):566-7.

[Cellular immunity in childhood iron deficiency anemia with recurrent respiratory infections]

[Article in Chinese]

Liu W, **Jiang A**, **Guo C**.

PLA No. 60 Hospital, Yunnan Dali 671003.

OBJECTIVE: To examine interleukin-2 (IL-2) activity,serum soluble IL-2 receptor (sIL-2R) level and T lymphocyte subsets in peripheral blood from 63 childhood iron deficiency anemia (IDA) patients with recurrent respiratory infections(RRI). METHODS: IL-2 activity, sIL-2R level and T lymphocyte subsets were assayed by MTT, ELISA and APAAP, respectively. RESULTS: IL-2 activity, percentages of CD3+ and CD4+ cells as well as the ratio of CD4+/ CD8+ cells in the patients were significantly lower ($P < 0.01$),while sIL-2R levels were higher than that in normal controls ($P < 0.01$). No significant change was found in the percentage of CD8+ cells. CONCLUSION: Cellular immunity was impaired in childhood IDA with RRI.

Publication Types:

- English Abstract

PMID: 15625892 [PubMed - in process]

Nat Rev Microbiol. 2004 Dec;2(12):946-53.

Iron and microbial infection.

Schaible UE, **Kaufmann SH**.

Max-Planck-Institute for Infection Biology, Department of Immunology, Schumannstrasse 21-22, D-10117, Berlin, Germany.

The use of iron as a cofactor in basic metabolic pathways is essential to both pathogenic microorganisms and their hosts. It is also a pivotal component of the innate immune response through its role in the generation of toxic oxygen and nitrogen intermediates. During evolution, the shared requirement of micro- and macroorganisms for this important nutrient has shaped the pathogen-host relationship. Here, we discuss how pathogens compete with the host for iron, and also how the host uses iron to counteract this threat.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 15550940 [PubMed - indexed for MEDLINE]

Nature. 2004 Dec 16;432(7019):917-21. Epub 2004 Nov 7.

Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron.

Flo TH, **Smith KD**, **Sato S**, **Rodriguez DJ**, **Holmes MA**, **Strong RK**, **Akira S**, **Aderem A**.

Institute for Systems Biology, Seattle, Washington 98103, USA.

Although iron is required to sustain life, its free concentration and metabolism have to be tightly regulated. This is achieved through a variety of iron-binding proteins including transferrin and ferritin. During infection, bacteria acquire much of their iron from the host by synthesizing siderophores that scavenge iron and transport it into the pathogen. We recently demonstrated that enterochelin, a bacterial catecholate siderophore, binds to the host protein lipocalin 2 (ref. 5). Here, we show that this event is pivotal in the innate immune response to bacterial infection. Upon encountering invading bacteria the Toll-like receptors on immune cells stimulate the transcription, translation and secretion of lipocalin 2; secreted lipocalin 2 then limits bacterial growth by sequestrating the iron-laden siderophore. Our finding represents a new component of the innate immune system and the acute phase response to infection.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15531878 [PubMed - indexed for MEDLINE]

J Vet Med B Infect Dis Vet Public Health. 2004 Jun;51(5):231-7.

Impairment of the peripheral lymphoid compartment in iron-deficient piglets.

Svoboda M, **Drabek J**, **Krejci J**, **Rehakova Z**, **Faldyna M**.

University of Veterinary and Pharmaceutical Sciences Clinic of Swine Diseases, Palackého 1-3, 612 42 Brno, Czech Republic. svobodama@vfu.cz

The aim of this study was to investigate the effect of neonatal iron deficiency on immune functions in young piglets. While control piglets were not given any iron preparation until the age of 21 days, another group of piglets was given 200 mg of Fe(3+)-dextran i.m. on day 3. Red blood cell parameters in the former, iron-deficient group were characteristic of hypochromic anaemia. In addition, the total leucocyte count ($P < 0.01$), relative and absolute neutrophil count ($P < 0.01$) and absolute lymphocyte count ($P < 0.05$) in peripheral blood were found significantly lower in iron-deficient piglets than in their iron-supplemented counterparts. Lymphocyte activity as measured by in vitro lymphocyte transformation test was impaired in iron-deficient piglets. A statistically significant decrease in circulating B-lymphocyte numbers was found in non-supplemented animals. Iron deficiency apparently negatively influenced the immunocompetence in piglets.

Publication Types:

- Clinical Trial
- Controlled Clinical Trial
- Research Support, Non-U.S. Gov't

PMID: 15330983 [PubMed - indexed for MEDLINE]

Cytokine. 2004 Apr 21;26(2):73-81.

Differential effects of iron deficiency and underfeeding on serum levels of interleukin-10, interleukin-12p40, and interferon-gamma in mice.

Kuvibidila S, **Warrier RP**.

Department of Pediatrics, Division of Research, Louisiana State University Health Sciences Center, and The Research Institute for Children, 1542 Tulane Avenue, Box T8-1, New Orleans, LA 70112, United States. skuvib@lsuhsc.edu

BACKGROUND: Over-production of interferon-gamma (IFN-gamma) and under-production of interleukin-10 (IL-10) are associated with autoimmunity, whereas the opposite is associated with overwhelming infections. The influence of iron deficiency, a public health problem for children on in vivo secretion of these cytokines has not been previously investigated. OBJECTIVE: To determine whether iron deficiency alters serum levels of IFN-gamma, IL-10, and IL-12 in mice. DESIGN AND METHODS: Cytokine levels were measured by enzyme immunoassay in iron-deficient (ID), control (C), pair-fed (PF), and iron replete C57BL/6 mice for 3 (R3) and 14 (R14) days (n = 24-28, 12 R14). RESULTS: Iron deficiency was associated with > or = 50% reduction in hemoglobin, hematocrit, liver iron stores, and thymus weight ($p < 0.05$). Iron repletion improved these measurements. While iron deficiency significantly reduced IL-12p40 (64%) and IFN-gamma (66%) levels, underfeeding reduced those of IL-10 (48%) ($p < 0.05$). Iron repletion improved cytokine concentrations to PF levels. Thymus atrophy observed in 16 ID and 19 R3 mice, had no effect on IL-12p40 and IFN-gamma, whereas it further decreased IL-10 levels by 72% ($p < 0.05$). Cytokine levels positively correlated with indicators of iron status, body and thymus weights ($r < or = 0.688$, $p < 0.05$). CONCLUSION: Data suggest that iron deficiency alters the balance between pro- and anti-inflammatory cytokines, a change that may affect innate and cell-mediated immunity, and risk of autoimmune disorders.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15050607 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2004 Mar;79(3):516-21.

Immune function is impaired in iron-deficient, homebound, older women.

Ahluwalia N, **Sun J**, **Krause D**, **Mastro A**, **Handte G**.

Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA 16802, USA.

BACKGROUND: Aging is often associated with a dysregulation of immune function. Iron deficiency may further impair immunity in older adults. Published reports on iron deficiency and immune response in humans are inconsistent. Most studies are focused on young children in developing countries and are often confounded by comorbid conditions, infections, and nutrient deficiencies. OBJECTIVE: Our objective was to determine the relation of iron status with immune function in homebound older women, who often have impairments in both iron status and immune response. The subjects were selected according to rigorous exclusion criteria for disease, infection, and deficiencies in key nutrients known to affect immunocompetence. DESIGN: Seventy-two homebound elderly women provided blood for comprehensive evaluation of iron status and cell-mediated and innate immunity. Women were classified as iron-deficient or iron-sufficient on the basis of multiple abnormal iron status test results. Groups were compared with respect to lymphocyte subsets, phagocytosis, oxidative burst capacity, and T cell proliferation upon stimulation with mitogens. RESULTS: In iron-deficient women, T cell proliferation upon stimulation with concanavalin A and phytohemagglutinin A was only 40-50% of that in iron-sufficient women. Phagocytosis did not differ significantly between the 2 groups, but respiratory burst was significantly less (by 28%) in iron-deficient women than in iron-sufficient women. CONCLUSIONS: Iron deficiency is associated with impairments in cell-mediated and innate immunity and may render older adults more vulnerable to infections. Further prospective studies using similar exclusion criteria for disease, infection, and concomitant nutrient deficiencies are needed for simultaneous examination of the effects of iron deficiency on immune response and morbidity.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 14985230 [PubMed - indexed for MEDLINE]

J Cell Biochem. 2003 Oct 1;90(2):278-86.

Effects of iron deficiency on the secretion of interleukin-10 by mitogen-activated and non-activated murine spleen cells.

Kuvibidila S, **Yu L**, **Ode D**, **Velez M**, **Gardner R**, **Warrier RP**.

Department of Pediatrics, Division of Research, Louisiana State University Health Sciences Center, Research Institute for Children, 1542 Tulane Avenue, New Orleans, Louisiana 70112, USA. skuvib@lsuhsc.edu

Interleukin (IL)-10 plays crucial regulatory roles in immune responses by inhibiting the secretion of several cytokines (IL-2, IL-12, interferon-gamma (IFN-gamma)) and lymphocyte proliferation. Iron deficiency, a public health problem for children, alters these immune responses. To determine whether these changes are related to altered IL-10 secretion, we measured IL-10 in 24 and 48 h supernatant of spleen cell cultures from iron deficient (ID), control (C), pairfed (PF), and ID mice fed the control diet (iron repletion) for 3 (R3) and 14 (R14) days (d, n = 12/group). Mean levels of hemoglobin, hematocrit, and liver iron stores varied as follows: C approximately equal PF approximately equal R14 > R3 > ID ($P < 0.01$). Mean baseline IL-10 levels of ID mice tended to be higher than those of other groups ($P > 0.05$, ANOVA). Mean IL-10 levels secreted by concanavalin A (Con A) and antibody raised against cluster of differentiation molecule 3 (anti-CD3)-treated cells (+/-background) were lower in ID than in C (48 h) and iron replete mice ($P < 0.05$). Underfeeding also reduced IL-10 secretion by anti-CD3-treated cells (48 h, $P < 0.05$). Lymphocyte proliferative responses to anti-CD3 +/- anti-CD28 antibodies were lower in ID than in C and PF mice, and they were corrected by iron repletion ($P < 0.05$). IL-10 levels negatively correlated with indicators of iron status (r <or= -0.285) and lymphocyte proliferation (r <or= -0.379 [r <or= -0.743 for ID mice]), but positively correlated with IFN-gamma levels (r <or= 0.47; $P < 0.05$). Data suggest that iron deficiency has a generalized deleterious effect on cells that secrete both cytokines. Reduced IL-10 secretion by activated cells does not overcome the inhibition of lymphocyte proliferation due to other factors of T cell activation that are regulated by iron.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 14505344 [PubMed - indexed for MEDLINE]

Iron and Cognitive Function

Arzneimittelforschung. 2007;57(6A):426-30.

Effects of iron deficiency anemia on cognitive function in children.

Agaoglu L, **Torun O**, **Unuvar E**, **Sefil Y**, **Demir D**.

Department of Pediatrics, Istanbul Faculty of Medicine, Istanbul University, Capa, Istanbul, Turkey. leyla.agaoglu@gmail.com

OBJECTIVE: To examine the effects of iron deficiency anemia on cognitive function and intelligence in children. METHODS: Matched case-control study was carried out with 30 children (aged 6-12 years) with iron deficiency anemia (IDA) but without any chronic disease and with normal neuromotor development. The WISC-R intelligence test was performed before and after 4-6 months of iron/vitamin treatment (5 mg iron/kg/day as iron(III)-hydroxide polymaltose complex, IPC, and multivitamin preparation). Pre- and post-treatment IQ scores of the IDA group were evaluated and compared to the control group. RESULTS: Treatment and control groups were similar in terms of age and gender (mean age 9.1 +/- 1.9 years for IDA group, 8.8 +/- 1.5 years for controls, 37 % versus 40 % girls, respectively). Mean total IQ score of the IDA group was 12.9 points lower than that of the control group and this was statistically significant ($p < 0.01$). Although a highly significant increase of 4.8 points in total IQ was found after treatment with IPC in the IDA group ($p < 0.01$), post-treatment mean total IQ score of the IDA group was 8.2 points lower than that of the control group. However this difference of 8.2 points was not statistically significant ($p > 0.05$). There were significant differences in the subtests of WISC-R between the pre-treatment IDA group and the control group. A significant improvement was found especially in these subtests following treatment. CONCLUSION: Iron deficiency anemia in children can affect long-term cognitive function. The WISC-R intelligence test subsets and pre- and post-treatment IQ scores of the IDA group were significantly differing from control group.

PMID: 17691592 [PubMed - indexed for MEDLINE]

J Pediatr Gastroenterol Nutr. 2009 Mar;48 Suppl 1:S8-15.

Sleep and neurofunctions throughout child development: lasting effects of early iron deficiency.

Peirano PD, **Algarín CR**, **Chamorro R**, **Reyes S**, **Garrido MI**, **Duran S**, **Lozoff B**.

Sleep and Functional Neurobiology Laboratory, Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile. ppeirano@inta.cl

Iron-deficiency anemia (IDA) continues to be the most common single nutrient deficiency in the world. Infants are at particular risk due to rapid growth and limited dietary sources of iron. An estimated 20% to 25% of the world's infants have IDA, with at least as many having iron deficiency without anemia. High prevalence is found primarily in developing countries, but also among poor, minority, and immigrant groups in developed ones. Infants with IDA test lower in mental and motor development assessments and show affective differences. After iron therapy, follow-up studies point to long-lasting differences in several domains. Neurofunctional studies showed slower neural transmission in the auditory system despite 1 year of iron therapy in IDA infants; they still had slower transmission in both the auditory and visual systems at preschool age. Different motor activity patterning in all sleep-waking states and several differences in sleep states organization were reported. Persistent sleep and neurofunctional effects could contribute to reduced potential for optimal behavioral and cognitive outcomes in children with a history of IDA.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't
- Review

PMID: 19214058 [PubMed - indexed for MEDLINE]

Dev Psychobiol. 2009 Apr;51(3):301-9.

A history of iron deficiency anemia during infancy alters brain monoamine activity later in juvenile monkeys.

Coe CL, **Lubach GR**, **Bianco L**, **Beard JL**.

Harlow Center for Biological Psychology, University of Wisconsin, 22 North Charter Street, Madison, WI 53715, USA. ccoe@wisc.edu

Both during and after a period of iron deficiency (ID), iron-dependent neural processes are affected, which raises the potential concern that the anemia commonly experienced by many growing infants could have a protracted effect on the developing brain. To further investigate the effects of ID on the immature brain, 49 infant rhesus monkeys were evaluated across the first year of life. The mothers, and subsequently the infants after weaning, were maintained on a standardized diet containing 180 mg/kg of iron and were not provided other iron-rich foods as treats or supplements. As the infants grew, they were all screened with hematological tests, which documented that 16 (33.3%) became markedly ID between 4 and 8 months of age. During this anemic period and subsequently at 1 year of age, cerebrospinal fluid (CSF) specimens were collected to compare monoamine activity in the ID and iron-sufficient infants. Monoamine neurotransmitters and metabolite levels were normal at 4 and 8 months of age, but by 1 year the formerly anemic monkeys had significantly lower dopamine and significantly higher norepinephrine levels. These findings indicate that ID can affect the developmental trajectory of these two important neurotransmitter systems, which are associated with emotionality and behavioral performance, and further that the impact in the young monkey was most evident during the period of recovery. (c) 2009 Wiley Periodicals, Inc.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 19194962 [PubMed - in process]

J Nutr. 2008 Dec;138(12):2495-501.

Early-life iron deficiency anemia alters neurotrophic factor expression and hippocampal neuron differentiation in male rats.

Tran PV, **Carlson ES**, **Fretham SJ**, **Georgieff MK**.

Department of Pediatrics, Center for Neurobehavioral Development, University of Minnesota, Minneapolis, MN 55455, USA.

Fetal-neonatal iron deficiency alters hippocampal neuronal morphology, reduces its volume, and is associated with acute and long-term learning impairments. However, neither the effects of early-life iron deficiency anemia on growth, differentiation, and survival of hippocampal neurons nor regulation of the neurotrophic factors that mediate these processes has been investigated. We compared hippocampal expression of neurotrophic factors in male rats made iron deficient (ID) from gestational d 2 to postnatal d (P) 7 to iron-sufficient controls at P7, 15, and 30 with quantitative RT-PCR, Western analysis, and immunohistology. Iron deficiency downregulated brain-derived neurotrophic factor (BDNF) expression in the hippocampus without compensatory upregulation of its specific receptor, tyrosine-receptor kinase B. Consistent with low overall BDNF activity, we found lower expression of early-growth response gene-1 and -2, transcriptional targets of BDNF signaling. Doublecortin expression, a marker of differentiating neurons, was reduced during peak iron deficiency, suggesting impaired neuronal differentiation in the ID hippocampus. In contrast, iron deficiency upregulated hippocampal nerve growth factor, epidermal growth factor, and glial-derived neurotrophic factor accompanied by an increase in neurotrophic receptor p75 expression. Our findings suggest that fetal-neonatal iron deficiency lowers BDNF function and impairs neuronal differentiation in the hippocampus.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 19022978 [PubMed - indexed for MEDLINE]

Neurotox Res. 2008 Aug;14(1):45-56.

Brain iron deficiency and excess; cognitive impairment and neurodegeneration with involvement of striatum and hippocampus.

Youdim MB.

Eve Topf and USA National Parkinson Foundation, Centers of Excellence for Neurodegenerative Diseases Research and Department of Pharmacology, Rappaport Family Research Institute, Technion-Faculty of Medicine, Haifa, Israel.
youdim@tx.technion.ac.il

While iron deficiency is not perceived as a life threatening disorder, it is the most prevalent nutritional abnormality in the world, and a better understanding of modes and sites of action, can help devise better treatment programs for those who suffer from it. Nowhere is this more important than in infants and children that make up the bulk of iron deficiency in society. Although the effects of iron deficiency have been extensively studied in systemic organs, until very recently little attention was paid to its effects on brain function. The studies of Oski at Johns Hopkin Medical School in 1974, demonstrating the impairment of learning in young school children with iron deficiency, prompted us to study its relevance to brain biochemistry and function in an animal model of iron deficiency. Indeed, rats made iron deficient have lowered brain iron and impaired behaviours including learning. This can become irreversible especially in newborns, even after long-term iron supplementation. We have shown that in this condition it is the brain striatal dopaminergic-opiate system which becomes defective, resulting in alterations in circadian behaviours, cognitive impairment and neurochemical changes closely associated with them. More recently we have extended these studies and have established that cognitive impairment may be closely associated with neuroanatomical damage and zinc metabolism in the hippocampus due to iron deficiency, and which may result from abnormal cholinergic function. The hippocampus is the focus of many studies today, since this brain structure has high zinc concentration and is highly involved in many forms of cognitive deficits as a consequence of cholinergic deficiency and has achieved prominence because of dementia in ageing and Alzheimer's disease. Thus, it is now apparent that cognitive impairment may not be attributed to a single neurotransmitter, but rather, alterations and interactions of several systems in different brain regions. In animal models of iron deficiency it is apparent that dopaminergic interaction with the opiate system and cholinergic neurotransmission may be defective.

PMID: 18790724 [PubMed - indexed for MEDLINE]

Brain Res. 2008 Oct 27;1237:75-83. Epub 2008 Aug 7.

Iron deficiency alters expression of genes implicated in Alzheimer disease pathogenesis.

Carlson ES, **Magid R**, **Petryk A**, **Georgieff MK**.

Department of Pediatrics, University of Minnesota School of Medicine, 420 Delaware Street SE, Minneapolis, MN 55455, USA.

Neonatal brain iron deficiency occurs after insufficient maternal dietary iron intake, maternal hypertension, and maternal diabetes mellitus and results in short and long-term neurologic and behavioral deficits. Early iron deficiency affects the genomic profile of the developing hippocampus that persists despite iron repletion. The purpose of the present study was threefold: 1) quantitative PCR confirmation of our previous microarray results, demonstrating upregulation of a network of genes leading to beta-amyloid production and implicated in Alzheimer disease etiology in iron-deficient anemic rat pups at the time of hippocampal differentiation; 2) investigation of the potential contributions of iron deficiency anemia and iron treatment to this differential gene expression in the hippocampus; and 3) investigation of these genes over a developmental time course in a mouse model where iron deficiency is limited to hippocampus, is not accompanied by anemia and is not repletable. Quantitative PCR confirmed altered regulation in 6 of 7 Alzheimer-related genes (Apbb1, C1qa, Clu, App, Cst3, Fn1, Htatip) in iron-deficient rats relative to iron-sufficient controls at P15. Comparison of untreated to treated iron-deficient animals at this age suggested the strong role of iron deficiency, not treatment, in the upregulation of this gene network. The non-anemic hippocampal iron-deficient mouse demonstrated upregulation of all 7 genes in this pathway from P5 to P25. Our results suggest a role for neonatal iron deficiency in dysregulation of genes that may set the stage for long-term neurodegenerative disease and that this may occur through a histone modification mechanism.

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PMCID: PMC2605272 [Available on 2009/10/27]

Eur Arch Psychiatry Clin Neurosci. 2008 Dec;258(8):489-96. Epub 2008 Jun 20.

Iron states and cognitive abilities in young adults: neuropsychological and neurophysiological assessment.

Khedr E, **Hamed SA**, **Elbeih E**, **El-Shereef H**, **Ahmad Y**, **Ahmed S**.

Department of Neurology and Psychiatry, Assiut University Hospital, P.O. Box 71516, Assiut, Egypt.

Many investigators found that iron deficiency anemia (IDA) had a great influence on cognitive functions in infants and children. However, studies of such topic in adults are few and controversial. We prospectively assessed the possible influence of IDA and iron supplementation (for 3 months) on cognitive function and intelligence of 28 young adults with IDA. We used group of hematological, cognitive, neurophysiological tests for assessment including: mini-mental state examination (MMSE), Wechsler memory scale-revised (WMS-R), Wechsler adult intelligence scale-revised (WAIS-R), event-related potentials (ERPs), and electroencephalography (EEG). Compared to controls, patients demonstrated lower scores of different cognitive tests (MMSE, WMS-R, and WAIS-R), which showed significant improvement after treatment. Prolongation of ERPs latencies (N200 and P300) and reduction in their amplitudes (P200 and P300) were identified with significant increase in amplitude occurred after treatment. EEG abnormalities were observed in 55% of patients which showed improvement in 35% after treatment. Positive correlation was identified before and after treatment between hemoglobin levels and MMSE (P=0.01, 0.05), total verbal (P=0.04) and performance (P=0.05, 0.04) IQ scores. Negative correlation was identified between before and after treatment between P300 latency and total IQ of WAIS-R (P=0.03, 0.008) and hemoglobin level (P=0.4, 0.01). Positive correlation was found before and after treatment between P300 amplitude and total IQ (P=0.028, 0.01) and serum iron (P=0.01, 0.001). In conclusion, IDA is a significant factor in cognitive performance in adult population, which can be partially reversed by treatment.

Publication Types:

- Clinical Trial

PMID: 18574611 [PubMed - indexed for MEDLINE]

Neurophysiol Clin. 2008 Apr;38(2):137-43. Epub 2008 Feb 21.

Quantitative EEG and cognitive evoked potentials in anemia.

Kececi H, **Degirmenci Y**.

Department of Neurology, Duzce University Medical Faculty, Duzce, Turkey. hulusikececi@dtip.edu.tr

OBJECTIVE: The anemic status may alter brain functions and electrogenesis, as reflected by EEG and cognitive EPs (CEPs). This study aims to evaluate CEPs and EEG power spectra in adult patients with iron-deficiency anemia and to determine the effects of appropriate iron therapy on electrodiagnostic findings. METHODS: Fifty-one patients with iron-deficiency anemia underwent CEP and EEG recording. All patients were re-assessed after three months of oral-iron therapy. RESULTS: All patients had recovered from their anemia through the three-month iron therapy. Central N1 amplitude and parietal P2 amplitude was increased. N2 latencies were shortened in frontal and central regions. P3 latencies were shortened in frontal, central and parietal areas and P3 amplitude was increased in the parietal region. Except in the gamma-band, all pretreatment and post-treatment mean-power values were significantly lower at the temporal, parietal and occipital regions. CONCLUSIONS: This study indicates that in iron-deficiency anemia, appropriate iron therapy can improve brain electrogenesis, as reflected by P300 and EEG power spectra.

PMID: 18423335 [PubMed - indexed for MEDLINE]

J Dev Behav Pediatr. 2008 Feb;29(1):11-7.

Selective impairment of cognitive performance in the young monkey following recovery from iron deficiency.

Lubach GR, **Coe CL**.

Harlow Center for Biological Psychology, Department of Psychology, University of Wisconsin, Madison, Wisconsin 53715, USA. grlubach@wisc.edu

OBJECTIVE: While poor nutrition during development is an obvious concern, the magnitude and duration of the neural and cognitive deficits that occur after moderate iron deficiency in infancy have remained controversial. A nonhuman primate model of infancy anemia was refined to investigate the effects on cognitive performance. METHODS: Young rhesus monkeys that experienced a delimited period of iron deficiency were tested on a series of cognitive tasks following normalization of their hematological status. Beginning at 8 to 9 months of age, 2 months after weaning from their mothers and consumption of solid food, the previously iron-deficient (ID) monkeys (n = 17) were compared to age- and gender-matched, iron-sufficient (IS) (n = 27) monkeys on a series of three tests of cognitive performance. Using the Wisconsin General Testing Apparatus, a Black/White Discrimination task was followed by acquisition of Black/White Reversal (BWR). RESULTS: ID monkeys were significantly slower at mastering the BWR task ($p < .04$), which required reversing and inhibiting the previously learned response. In addition, ID infants were significantly less object oriented ($p < .017$) and more distractible ($p < .018$). However, on two subsequent tests, the Concurrent Object Discrimination and Delayed Non-Match-to-Sample, there were no differences in acquisition, performance, or behavioral reactivity. CONCLUSIONS: The initial cognitive and behavioral deficits are similar to those seen in follow-up evaluations of anemic children, but the limited extent of the impairment after this moderate iron deficiency that involved a select nutrient deficiency is encouraging for the benefits attainable through early identification and iron supplementation.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 18300719 [PubMed - indexed for MEDLINE]

Biochem Soc Trans. 2008 Dec;36(Pt 6):1267-71.

The role of iron in neurodevelopment: fetal iron deficiency and the developing hippocampus.

Georgieff MK.

Department of Pediatrics, Division of Neonatology, University of Minnesota School of Medicine, Minneapolis, MN 55455, USA. georg001@umn.edu

Iron is a ubiquitous nutrient that is necessary for normal neurodevelopment. Gestational conditions that compromise fetal iron status include maternal iron deficiency, smoking, diabetes mellitus and hypertension. The iron-deficient neonate has altered recognition memory function and temperament while iron-deficient. The memory deficits persist even after iron repletion. Animal models demonstrate that early iron deficiency affects neuronal and glial energy metabolism, monoamine metabolism and myelination, consistent with behavioural findings in human infants. Of particular recent interest are genomic changes in transcripts coding for signal transduction, dendritic structure and energy metabolism induced by early iron deficiency that last well into adulthood in spite of iron treatment. Early iron sufficiency is critical for long-term neurological health.

Publication Types:

- Research Support, N.I.H., Extramural
- Review

PMID: 19021538 [PubMed - indexed for MEDLINE]

Mult Scler. 2008 Jun;14(5):602-8. Epub 2008 Apr 11.

The role of iron dysregulation in the pathogenesis of multiple sclerosis: an Egyptian study.

Abo-Krysha N, **Rashed L**.

Department of Neurology, Cairo University, Cairo, Egypt. nhtaha@yahoo.com

BACKGROUND: Iron is essential for virtually all types of cells and organisms. The significance of iron for brain function is reflected by the presence of receptors for transferrin on brain capillary endothelial cells. Iron imbalance is associated with proinflammatory cytokines and oxidative stress, which have been implicated in the pathogenesis of multiple sclerosis (MS). Transferrin receptor (TfR) is the major mediator of iron uptake. Its expression is increased to facilitate iron entrance into the cell. The increased serum level of soluble transferrin receptor (sTfR) may indicate an abnormal intracellular distribution of iron and a decrease in the cytoplasmic compartment. OBJECTIVE: Our objective is to assess the possible role of iron metabolism dysfunction in the pathogenesis of MS. METHODS: Thirty subjects were selected from the Neurology Department of Kasr El-Aini hospital, Cairo University: 20 MS patients, where nine patients were relapsing and progressive (secondary progressive (SP) of which six were secondary progressive active (SP-A) and three were secondary progressive stable (SP-S)), seven were relapsing-remitting active (RR-A) and four were primary progressive (PP); and 10 control subjects matched in age and sex. Each patient was subjected to a thorough general medical and neurological examination, Kurtzke MS rating scales, laboratory assessment, neuro-imaging, evoked potentials and quantitative determination of the indices of iron metabolism, such as serum iron and sTfR. RESULTS: The serum level of sTfR was significantly higher in our MS patients compared with the control group ($p = 0.0001$). The levels were significantly higher in SP-A ($p = 0.001$), SP-S ($p = 0.01$), RR-A ($p = 0.0001$) and PP ($p = 0.003$) patients than in controls. Iron values were within normal limits in all patients. The increased serum sTfR level in non-anemic MS patients with active disease reflects the increased iron turnover. The elevation of sTfR levels in stable patients may indicate active inflammation with ongoing oxidative damage that is not detectable by history or examination. CONCLUSIONS: Iron overload and upregulation of iron-handling proteins, such as TfR, in the MS brain can contribute to pathogenesis of Multiple Sclerosis and iron imbalance is associated with a pro-oxidative stress and a proinflammatory environment, this suggest that iron could be a target for MS therapy to improve neuronal iron metabolism.

PMID: 18408021 [PubMed - indexed for MEDLINE]

Early Hum Dev. 2008 Jul;84(7):479-85. Epub 2008 Feb 12.

Iron deficiency and infant motor development.

Shafir T, **Angulo-Barroso R**, **Jing Y**, **Angelilli ML**, **Jacobson SW**, **Lozoff B**.

Center for Human Growth and Development, University of Michigan, Ann Arbor, Michigan 48109-5406, USA.

BACKGROUND: Iron deficiency (ID) during early development impairs myelination and basal ganglia function in animal models. AIMS: To examine the effects of iron deficiency anemia (IDA) and iron deficiency (ID) without anemia on infant motor skills that are likely related to myelination and basal ganglia function. STUDY DESIGN: Observational study. SUBJECTS: Full-term inner-city African-American 9- to 10-month-old infants who were free of acute or chronic health problems with iron status indicators ranging from IDA to iron sufficiency (n=106). Criteria for final iron status classification were met by 77 of these infants: 28 IDA, 28 non-anemic iron-deficient (NA ID), and 21 iron-sufficient (IS). OUTCOME MEASURES: Gross motor developmental milestones, Peabody Developmental Motor Scale, Infant Neurological International Battery (INFANIB), motor quality factor of the Bayley Behavioral Rating Scale, and a sequential/bi-manual coordination toy retrieval task. General linear model analyses tested for linear effects of iron status group and thresholds for effects. RESULTS: There were linear effects of iron status on developmental milestones, Peabody gross motor (suggestive trend), INFANIB standing item, motor quality, and toy retrieval. The threshold for effects was ID with or without anemia for developmental milestones, INFANIB standing item, and motor quality and IDA for toy retrieval. CONCLUSIONS: Using a comprehensive and sensitive assessment of motor development, this study found poorer motor function in ID infants with and without anemia. Poorer motor function among non-anemic ID infants is particularly concerning, since ID without anemia is not detected by common screening procedures and is more widespread than IDA.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 18272298 [PubMed - indexed for MEDLINE]

Brain Res. 2006 May 30;1092(1):47-58. Epub 2006 May 2.

Cellular iron concentrations directly affect the expression levels of norepinephrine transporter in PC12 cells and rat brain tissue.

Beard JL, **Wiesinger JA**, **Jones BC**.

Department of Nutritional Science, S-128 Henderson South Building, The Pennsylvania State University, University Park, PA 16802, USA. jbeard@psu.edu

Neurological development and functioning are adversely affected by iron deficiency in early life. Iron-deficient rats are known to have elevations in extracellular DA and NE, suggesting alterations in reuptake of these monoamines. To explore possible mechanisms by which cellular iron concentrations may alter NE transporter functioning, we utilized NET expressing PC12 cells and iron-deficient rats to explore the relationship between NET protein and mRNA expression patterns and iron concentrations. Treatment of PC12 with the iron chelator, desferrioxamine mesylate (DFO, 50 microM for 24 h), significantly decreased [3H] NE uptake by more than 35% with no apparent change in Km. PC12 cells exposed to increasing concentrations of DFO (25-100 microM) exhibited a dose response decrease in [3H] NE uptake within 24 h (38-73% of control) that paralleled a decrease in cellular NET protein content. Inhibition of protein synthesis with cycloheximide resulted in NET disappearance rates from DFO-treated cells greatly exceeding the rate of loss from control cells. RT-PCR analysis revealed only a modest decrease in NET mRNA levels. Rat brain locus ceruleus and thalamus NET mRNA levels were also only modestly decreased (10-15%) despite a 40% reduction in regional brain iron. In contrast, NET proteins levels in thalamus and locus ceruleus were strongly affected by regional iron deficiency with high correlations with iron concentrations ($r > 0.94$ and $r > 0.80$ respectively). The present findings demonstrate that NET protein concentrations and functioning are dramatically reduced with iron deficiency; the modest effect on mRNA levels suggests a stronger influence on NET trafficking and degradation than on protein synthesis.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 16650837 [PubMed - indexed for MEDLINE]

Brain Res. 2008 Oct 27;1237:75-83. Epub 2008 Aug 7.

Iron deficiency alters expression of genes implicated in Alzheimer disease pathogenesis.

Carlson ES, **Magid R**, **Petryk A**, **Georgieff MK**.

Department of Pediatrics, University of Minnesota School of Medicine, 420 Delaware Street SE, Minneapolis, MN 55455, USA.

Neonatal brain iron deficiency occurs after insufficient maternal dietary iron intake, maternal hypertension, and maternal diabetes mellitus and results in short and long-term neurologic and behavioral deficits. Early iron deficiency affects the genomic profile of the developing hippocampus that persists despite iron repletion. The purpose of the present study was threefold: 1) quantitative PCR confirmation of our previous microarray results, demonstrating upregulation of a network of genes leading to beta-amyloid production and implicated in Alzheimer disease etiology in iron-deficient anemic rat pups at the time of hippocampal differentiation; 2) investigation of the potential contributions of iron deficiency anemia and iron treatment to this differential gene expression in the hippocampus; and 3) investigation of these genes over a developmental time course in a mouse model where iron deficiency is limited to hippocampus, is not accompanied by anemia and is not repletable. Quantitative PCR confirmed altered regulation in 6 of 7 Alzheimer-related genes (Apbb1, C1qa, Clu, App, Cst3, Fn1, Htatip) in iron-deficient rats relative to iron-sufficient controls at P15. Comparison of untreated to treated iron-deficient animals at this age suggested the strong role of iron deficiency, not treatment, in the upregulation of this gene network. The non-anemic hippocampal iron-deficient mouse demonstrated upregulation of all 7 genes in this pathway from P5 to P25. Our results suggest a role for neonatal iron deficiency in dysregulation of genes that may set the stage for long-term neurodegenerative disease and that this may occur through a histone modification mechanism.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 18723004 [PubMed - indexed for MEDLINE]

PMCID: PMC2605272 [Available on 2009/10/27]

Am J Clin Nutr. 2007 Mar;85(3):778-87.

Iron treatment normalizes cognitive functioning in young women.

Murray-Kolb LE, **Beard JL**.

Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA. lmurrayk@jhsph.edu

BACKGROUND: Evidence suggests that brain iron deficiency at any time in life may disrupt metabolic processes and subsequently change cognitive and behavioral functioning. Women of reproductive age are among those most vulnerable to iron deficiency and may be at high risk for cognitive alterations due to iron deficiency. OBJECTIVE: We aimed to examine the relation between iron status and cognitive abilities in young women. DESIGN: A blinded, placebo-controlled, stratified intervention study was conducted in women aged 18-35 y of varied iron status who were randomly assigned to receive iron supplements or a placebo. Cognition was assessed by using 8 cognitive performance tasks (from Detterman's Cognitive Abilities Test) at baseline (n = 149) and after 16 wk of treatment (n = 113). RESULTS: At baseline, the iron-sufficient women (n = 42) performed better on cognitive tasks (P = 0.011) and completed them faster (P = 0.038) than did the women with iron deficiency anemia (n = 34). Factors representing performance accuracy and the time needed to complete the tasks by the iron-deficient but nonanemic women (n = 73) were intermediate between the 2 extremes of iron status. After treatment, a significant improvement in serum ferritin was associated with a 5-7-fold improvement in cognitive performance, whereas a significant improvement in hemoglobin was related to improved speed in completing the cognitive tasks. CONCLUSIONS: Iron status is a significant factor in cognitive performance in women of reproductive age. Severity of anemia primarily affects processing speed, and severity of iron deficiency affects accuracy of cognitive function over a broad range of tasks. Thus, the effects of iron deficiency on cognition are not limited to the developing brain.

Publication Types:

- Randomized Controlled Trial
- Research Support, N.I.H., Extramural
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 17344500 [PubMed - indexed for MEDLINE]

Trace Elem Res. 2007 Winter;120(1-3):92-101.

Acquisition of visuomotor abilities and intellectual quotient in children aged 4-10 years: relationship with micronutrient nutritional status.

González HF, **Malpeli A**, **Etchegoyen G**, **Lucero L**, **Romero F**, **Lagunas C**, **Lailhacar G**, **Olivares M**, **Uauy R**.

Instituto de Desarrollo e Investigaciones Pediátricas, Centro Asociado a la Comisión de Investigaciones Científicas de la Provincia de Buenos Aires, Hospital de Niños Sor María Ludovica, La Plata, Argentina.
horaciofgonzalez@gmail.com

Lethargy, poor attention, and the high rate and severity of infections in malnourished children affect their educational achievement. We therefore studied the association between visuomotor abilities and intelligence quotient (IQ) and their relationship with iron, zinc, and copper. A cross-sectional study was carried out on a sample of 89 healthy children (age range, 4-10 years). Evaluations of visuomotor ability and IQ were performed with the Developmental Test of Visual Motor Integration (VMI) and the Scale for Measurement of Intelligence for children aged 3-18 years, respectively. Nutritional status was assessed using anthropometry and biochemical assessments, which included serum ferritin, zinc and copper levels, and Hb. The sample was classified as having low or normal VMI scores: 47 children (52.8%, mean age 7 +/- 1.5 years) had low VMI, and 42 (47.2%, mean age 7 +/- 2.06 years) had normal VMI. There were no statistically significant differences in socioeconomic and cultural condition between both groups. We found significantly higher serum copper and ferritin levels in normal as compared to low VMI, but we did not find any differences with zinc. IQ was significantly higher in normal vs low VMI children. The fact that children with abnormal VMI presented low mean serum copper and ferritin concentrations could indicate that copper and iron deficiencies in this sample could be related with visuomotor abilities.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17916959 [PubMed - indexed for MEDLINE]

J Nutr. 2004 Sep;134(9):2349-54.

Once-weekly and 5-days a week iron supplementation differentially affect cognitive function but not school performance in Thai children.

Sungthong R, **Mo-suwan L**, **Chongsuvivatwong V**, **Geater AF**.

Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Songkla 90110, Thailand. rassamee@ratree.psu.ac.th

Many studies have reported comparable hemoglobin response in subjects given intermittent and daily iron supplements. However, the effect of intermittent iron supplementation on impaired cognitive function, one of the serious consequences of iron deficiency among children, has not been studied. We investigated the effects of 1 d/wk (weekly) and 5 d/wk (daily) iron supplementation on changes in results of intelligence quotient (IQ), Thai language, and mathematics tests among Thai primary schoolchildren. A double-blind, randomized, placebo-controlled trial was conducted. Primary schoolchildren (n = 397) were randomly assigned to receive iron supplements daily or weekly or placebo. Ferrous sulfate (300 mg) or placebo tablets were given under direct observation by the researcher for 16 wk. Changes in IQ, and Thai language and mathematics scores were then compared. The increases in hemoglobin concentration were comparable in the weekly and daily iron supplementation groups but serum ferritin increased more in the children supplemented daily. Children receiving daily iron supplements, however, had a significantly lower increase in IQ (3 +/- 12 points) than those receiving the supplement weekly (6 +/- 12 points) or placebo (6 +/- 12 points), whereas the last-mentioned two groups did not differ. Z-scores of Thai language and mathematics test results did not differ among the groups. We conclude that weekly iron supplementation is the regimen of choice in this study community.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 15333727 [PubMed - indexed for MEDLINE]

Eur J Clin Nutr. 2004 Nov;58(11):1532-42.

Effect of iron supplementation on cognition in Greek preschoolers.

Metallinos-Katsaras E, **Valassi-Adam E**, **Dewey KG**, **Lönnerdal B**, **Stamoulakatou A**, **Pollitt E**.

Simmons College, Boston, MA 02132, USA. metallin@simmons.edu

OBJECTIVE: To examine effects of iron supplementation on vigilance, attention and conceptual learning in preschool children in Greece. DESIGN: Randomized Double-Blind Placebo Controlled trial of iron. Randomization stratified by iron status and day care center (DCC). SETTING: Nine public DCCs in Athens, Greece. SUBJECTS: In all, 49 3-4-y olds (21 anemic, 28 good iron status) with birth weight not less than 2500 g, currently healthy; benign past medical history, IQ > or =1 s.d. below the age-adjusted mean, serum Pb < or =200 ppb (none exceeded 50 ppb), and height, weight and head circumference for age > or =10th percentile. Anemia defined as: (1) pretreatment Hgb <112 g/l and TS <16% and ferritin <12 microg/L OR (2) Hgb rise of >10 g/l (T2-T0) with iron supplementation. Good iron status was defined as baseline levels of Hgb >120 g/l and either TS >20% or serum ferritin >12 microg/l. INTERVENTION: The intervention consisted of a 2-month supplementation of 15 mg iron (and MV) vs placebo (MV alone). RESULTS: After iron treatment, the anemic subjects made significantly fewer errors of commission (14% higher specificity, P<0.05), exhibited 8% higher accuracy (P<0.05) and were significantly more efficient (mean difference=1.09, P<0.05) than those given placebo. These effects of iron were not found among preschoolers with good iron status. No effects of iron treatment were found on the Oddity Learning task. CONCLUSIONS: This study demonstrated that iron supplementation of iron-deficient anemic preschoolers results in an improvement in discrimination, specifically selective attention.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

PMID: 15226754 [PubMed - indexed for MEDLINE]

Asia Pac J Clin Nutr. 2002;11(2):117-22.

Effects of haemoglobin and serum ferritin on cognitive function in school children.

Sungthong R, **Mo-suwan L**, **Chongsuvivatwong V**.

Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand. sburapat@medicine.psu.ac.th

The association between iron deficiency anaemia and cognitive function impairment has been widely reported in young children, but whether the impairment is a result of iron deficiency per se or a combination of iron deficiency and anaemia, and how these conditions interact, is still questionable. Four hundred and twenty-seven school children from two schools in socioeconomically deprived communities were selected in southern Thailand. Iron status was determined by haemoglobin and serum ferritin concentrations. Cognitive function in this study was measured by IQ test and school performance, including Thai language and mathematics scores, using z-scores based on distributions within the same grade and school. Data on demography and socioeconomic status were collected by questionnaire answered by the parents. Linear regression models were used to investigate the effect of anaemia and iron deficiency, reflected by haemoglobin and serum ferritin concentration, on cognitive function and school performance. We found that cognitive function increased with increased haemoglobin concentration in children with iron deficiency, but did not change with haemoglobin concentration in children with normal serum ferritin level. Children with iron deficiency anaemia had consistently the poorest cognitive function (IQ, 74.6 points; Thai language score, 0.3 SD below average; and mathematics score, 0.5 SD below average). Children with non-anaemic iron deficiency but with high haemoglobin levels had significantly high cognitive function (IQ, 86.5 points; Thai language score, 0.8 SD above average; and mathematics score, 1.1 SD above average). This study found a dose-response relationship between haemoglobin and cognitive function in children with iron deficiency, whereas no similar evidence was found in iron sufficient children.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 12074177 [PubMed - indexed for MEDLINE]

Med Hypotheses. 2008;70(1):70-2. Epub 2007 Jun 18.

Iron deficiency anaemia influences cognitive functions.

Petranovic D, **Batinac T**, **Petranovic D**, **Ruzic A**, **Ruzic T**.

Department of Hematology, Rijeka University Hospital, Kresimirova 42, 51000 Rijeka, Croatia.

Many diseases, different nutritional, metabolic and hormonal changes, ageing and drugs can alter cognitive functions. Anemia via cerebral hypoxia and other possible mechanisms has been suggested to have a great influence on cognition. Iron deficiency anemia, the most common form of anemia, has been suggested to result in cognitive deterioration and alteration of neurological functions. Previous studies resulted in significant discrepancies considering correlation between anemia and cognitive achievement mainly because different or not sensitive enough tests used to measure cognition. We suggest a significant influence of iron deficiency anemia on dynamic properties and functional features of the central nervous system activity. Cognitive achievement is strongly related to hemoglobin level and could be expected in all patients. Higher hemoglobin level results in better CNS function. As a first step in confirming or refuting our hypotheses we suggest standardization of the method used to measure cognition, such as a very sensitive apparatus like Complex reactiometer Drenovac (CRD).

PMID: 17574345 [PubMed - indexed for MEDLINE]

Iron and Anemia

Transpl Int. 2009 Apr;22(4):434-40. Epub 2008 Dec 9.

Iron deficiency anemia and iron losses after renal transplantation.

Zheng S, **Coyne DW**, **Joist H**, **Schuessler R**, **Godboldo-Brooks A**, **Ercole P**, **Brennan DC**.

Department of Internal Medicine, Renal Division, Washington University School of Medicine, St Louis, MO 63110, USA.

Iron deficiency contributes to anemia after transplantation. The magnitude of iron loss from blood loss in the peri-transplantation period has not been quantified. We prospectively estimated phlebotomy and surgical losses over the first 12-weeks following transplantation in 39 consecutive renal transplant recipients on hemodialysis (HD), peritoneal dialysis (PD), or chronic kidney disease (CKD). At transplant, ferritin levels were <200 ng/ml in 51% of the patients, and iron saturation was </=20% in 44%. CKD patients more commonly had ferritin levels <200 ng/ml than either HD or PD patients (100% vs. 21% vs. 67%, P < 0.0002, respectively). Blood loss was similar among HD, PD and CKD patients (833 +/- 194 vs. 861 +/- 324 vs. 755 +/- 79 ml respectively, P = NS), and no difference between deceased and living donor transplant recipients (881 +/- 291 vs. 788 +/- 162 ml, P = 0.33). Based on baseline hemoglobin (Hgb) of 11.8 g/dl, we estimated that an additional 330 mg of iron was needed to normalize hemoglobin to 13 g/dl, and 605 mg to increase hemoglobin to 14 g/dl. Blood and iron losses over the first 12 weeks post-transplant are substantial and may warrant early administration of intravenous iron.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 19076330 [PubMed - indexed for MEDLINE]

Hematology. 2008 Dec;13(6):352-5.

Prevalence of iron deficiency anemia among adolescent schoolgirls from Kermanshah, Western Iran.

Akramipour R, **Rezaei M**, **Rahimi Z**.

Department of Pediatrics, Kermanshah University of Medical Sciences, Kermanshah, Iran.

Iron deficiency anemia is a major health problem in developing countries. Anemia reduces physical work capacity and cognitive function and adversely affects learning and scholastic performance in schoolgirls entering adolescence. A cross-sectional study was conducted to determine the prevalence of iron deficiency, iron deficiency anemia and anemia among adolescent school girls aged 14-20 years from 20 different high schools located in three educational areas of Kermanshah, the capital of Kermanshah province in Western Iran. The prevalence of anemia (Hb<12 mg/dl) among adolescent school girls was 21.4%. Iron deficiency using a ferritin level <12 microg/l was found in 23.7% of studied girls. There were 47 girls (12.2%) with iron deficiency anemia (Hb<12 g/dl and ferritin <20 microg/l). Around 57.3% of anemic girls were iron deficient. There were no significant differences between the presence of anemia and the level of education of parents. The mean levels of hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean cell hemoglobin (MCH) and mean cell hemoglobin concentration (MCHC) in studied adolescent girls from Western Iran were found to be lower than those reported for females aged 12-18 years. In conclusion, regarding the detrimental long-term effects and high prevalence of iron deficiency, iron deficiency anemia and anemia in Kermanshah, Western Iran its prevention could be a high priority in the programs of health system of the country and supplementation of a weekly iron dose is recommended.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 19055864 [PubMed - indexed for MEDLINE]

J Am Coll Nutr. 2008 Apr;27(2):229-43.

Determinants of anemia among preschool children in the Philippines.

Tengco LW, **Rayco-Solon P**, **Solon JA**, **Sarol JN Jr**, **Solon FS**.

Nutrition Center of the Philippines, Villamor Interchange, South Superhighway, Western Bicutan, Taguig City 1630, Philippines.

OBJECTIVE: Our objective was to identify the determinants of anemia among rural Filipino children aged 12-71 months. METHODS: A cross-sectional survey was conducted among 2090 preschool children from 8 rural villages in Cebu, an area non-endemic for malaria and schistosomiasis. Hemoglobin (Hb) concentration was determined using a HemoCue hemoglobinometer and zinc protoporphyrin (ZPP) concentration was measured with a hematofluorometer. A 3-day non-consecutive 24-hour food recall interview with the child's primary caregiver was done to estimate the child's dietary intake. Stool analysis for presence of soil-transmitted helminths was performed through a concentration technique. A separate interview on household socio-economic status with the child's primary caregiver was conducted. RESULTS: Mean Hb concentration was 12.0 g/dL (SD 1.3). 16.1% were anemic. Age and sex had a significant interaction in their effect on Hb concentration. Females had higher Hb concentration between 12 to 23 months of age. Hb levels equalize between the 2 genders at around 24 months and increase with similar increments until 71 months of age. All dietary parameters improved Hb concentration with increasing intake. In the multiple regression, however, only the index for bioavailable iron and vitamin C intakes remained independent factors. None of the helminths or combination of helminths had significant effects on Hb concentration. Among the socio-economic variables, maternal educational attainment and water supply were significant independent factors. Mean ZPP concentration was 72.07 (SD 46.45) and 30.8% were iron deficient. As with Hb concentration, age and sex had a significant interaction in their effect on ZPP concentration, with females having lower ZPP levels before 24 months of age. Bioavailable iron (animal iron + 0.3*plant iron) had a significant effect on ZPP concentration at levels of at least 15% of the iron requirement. This was seen even after controlling for multivitamin supplementation. CONCLUSION: The control of anemia among preschoolers can be achieved through a combination of various nutritional interventions such as micronutrient supplementation, food fortification and nutrition education. Our findings emphasize the importance of a multi-sectoral approach to nutritional problems--the importance of empowering women (through engagement and education) and of maintaining a healthy physical environment (water and sanitation) are often peripheral concerns of nutritionists. Our study highlights the importance of supporting initiatives that address these issues not only for their core benefit, but also for the potential benefit to nutrition.

PMID: 18689554 [PubMed - indexed for MEDLINE]

Heart Fail Rev. 2008 Dec;13(4):393-404. Epub 2008 Mar 25.

Iron and anemia in human biology: a review of mechanisms.

Handelman GJ, **Levin NW**.

Clinical Laboratory and Nutrition Sciences, University of Massachusetts, 3 Solomont Way, Lowell, MA 01854, USA. Garry_Handelman@uml.edu

The biology of iron in relation to anemia is best understood by a review of the iron cycle, since the majority of iron for erythropoiesis is provided by iron recovered from senescent erythrocytes. In iron-deficiency anemia, storage iron declines until iron delivery to the bone marrow is insufficient for erythropoiesis. This can be monitored with clinical indicators, beginning with low plasma ferritin, followed by decreased plasma iron and transferrin saturation, and culminating in red blood cells with low-Hb content. When adequate dietary iron is provided, these markers show return to normal, indicating a response to the dietary supplement. Anemia of inflammation (also known as anemia of chronic disease, or ACD) follows a different course, because in this form of anemia storage iron is often abundant but not available for erythropoiesis. The diagnosis of ACD is more difficult than the diagnosis of iron-deficiency anemia, and often the first identified symptom is the failure to show a response to a dietary iron supplement. Confirmation of ACD is best obtained from elevated markers of inflammation. The treatment of ACD, which typically employs erythropoietin (EPO) supplements and intravenous iron (i.v.-iron), is empirical and often falls shorts of therapeutic goals. Dialysis patients show a complex pattern of anemia, which results from inadequate EPO production by the kidney, inflammation, changes in nutrition, and blood losses during treatment. EPO and i.v.-iron are the mainstays of treatment. Patients with heart failure can be anemic, with incidence as high as 50%. The causes are multifactorial; inflammation now appears to be the primary cause of this form of anemia, with contributions from increased plasma volume, effects of drug therapy, and other complications of heart disease. Discerning the mechanisms of anemia for the heart failure patient may aid rational therapy in each case.

Publication Types:

- Review

PMID: 18363095 [PubMed - indexed for MEDLINE]

Toxicol Lett. 2008 Apr 1;177(3):156-67. Epub 2008 Jan 30.

Iron deficiency causes duodenum mucosal hyperplasia in male Wistar rats.

Cunha GC, **van Ravenzwaay B**, **Mellert W**, **Kaufmann W**.

BASF SE, Experimental Toxicology and Ecology, Z 470, 67056 Ludwigshafen, Germany.

Administration of an iron-deficient diet to Wistar rats resulted within 14 days in reduced serum iron concentrations, a microcytic hypochromic anemia, characteristic for impaired hemoglobin synthesis, and an increase of duodenal epithelial cell proliferation. After 5 weeks of iron deficiency, hypochromic microcytic anemia and a clear increase of duodenum weight but no pronounced effects on cell proliferation was observed. Increased duodenum weights corresponded to significant increases in mucosal area, indicating a diffuse, simple mucosal hyperplasia. The sequence of events following iron depletion thus appears to be: (1) reduced serum iron levels, (2) induction of hypochromic microcytic anemia, (3) increased duodenal epithelial cell proliferation, and (4) increased duodenal weight (increased mucosal area). Iron deficiency anemia was rapidly reversible after a 2-week recovery period. However, increased duodenum weights were still noted at that time. Intramuscular iron supplementation in animals fed with iron-deficient diet maintained body iron levels not below normal values, and neither anemia nor increased duodenum cell proliferation were detected after 14 days. A 5-week iron supplementation period resulted in slightly increased serum iron values, and slightly decreased duodenal epithelial cell proliferation. Thus, increased duodenum mucosal hyperplasia was shown to be secondary to depletion of body iron and anemia and reflects an attempt to increase iron absorption to counteract iron deficiency.

PMID: 18358645 [PubMed - indexed for MEDLINE]

Eur J Appl Physiol. 2008 Apr;102(6):703-9. Epub 2007 Dec 19.

Anemia and iron status in young fertile non-professional female athletes.

Di Santolo M, **Stel G**, **Banfi G**, **Gonano F**, **Cauci S**.

Department of Biomedical Sciences and Technologies, School of Medicine, University of Udine, Piazzale Kolbe 4, 33100 Udine, Italy.

We evaluated the effects of regular physical exercise on anemia and iron status in young non-professional female athletes. A total of 191 healthy white Italian women (23.5 +/- 4.68 years) were analyzed; 70 were non-professional athletes performing 11.1 +/- 2.63 h week(-1) exercise and 121 were sedentary controls. Blood markers of anemia and iron status-hemoglobin (Hb), hematocrit (Hct), red blood cells (RBC), serum ferritin, iron, transferrin (Tf), transferrin saturation (TfS), soluble transferrin receptor (sTfR), and the sTfR/log ferritin ratio (sTfR-F index)-were evaluated. Anemia threshold was Hb < 120 g l(-1). Ferritin concentrations < 12 microg l(-1) were considered as iron deficiency (ID). Frequency of anemia (15.7 versus 10.7%, P = 0.32), ID (27.1 versus 29.8%, P = 0.70), and ID anemia (8.6 versus 5.8%, P = 0.46) was not different in athletes and controls. However, athletes were threefold more likely than controls (17.1 versus 5.8%) to have serum iron < 50 microg dl(-1) [odds ratio (OR) 3.37, P = 0.012]. Low-TfS (<15%) was found in 25.7% of athletes and in 13.2% of controls, OR 2.27, P = 0.030. Elevated-sTfR (>1.76 mg l(-1)) was found in 24.3% of athletes and in 12.4% of controls, OR 2.27, P = 0.034. Regular non-professional sport activity does not cause an increased rate of anemia or of iron deficiency in fertile women. However, physical exercise has an impact on iron status as it reduces serum iron and transferrin saturation, and elevates sTfR. Nearly one fifth of recreational athletes have anemia and a third have iron deficit, these conditions can decrease their physical performance.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18092176 [PubMed - indexed for MEDLINE]

Am J Nephrol. 2007;27(6):565-71. Epub 2007 Sep 5.

Nonhematological benefits of iron.

Agarwal R.

Division of Nephrology, Department of Medicine, Indiana University School of Medicine, and Richard L. Roudebush VA Medical Center, Indianapolis, Indiana, USA. ragarwal@iupui.edu

Iron deficiency anemia is common in people with chronic kidney disease (CKD) and its importance in supporting erythropoiesis is unquestioned especially in those patients treated with erythropoietin. Clinical symptomatology such as fatigability, cold intolerance, failure to concentrate and poor effort intolerance is often attributed to anemia or uremia. That iron deficiency, per se, can cause these symptoms is poorly recognized. Clinical and animal studies that support the benefits of iron supplementation, independent of increasing hemoglobin, such as those on immune function, physical performance, thermoregulation, cognition, and restless leg syndrome and aluminum absorption is the subject of this narrative review. (c) 2007 S. Karger AG, Basel.

Publication Types:

- Review

PMID: 17804903 [PubMed - indexed for MEDLINE]

Indian J Pediatr. 2008 Apr;75(4):355-7. Epub 2008 May 18.

Iron deficiency anemia in an urban slum.

Hanumante NM, **Kanvinde S**, **Sanwalka NJ**, **Vaidya MV**, **Khadilkar AV**.

Poona Medical Foundation Research Center, Ruby Hall Clinic, Pune, India.

OBJECTIVE: Of this pilot study was to assess the iron status and dietary intake of 1-3 year-old apparently healthy toddlers of the lower socio-economic class, and the effect of eight weeks intervention with liquid oral iron in an urban slum in Pune, India. METHODS: 50 toddlers (M= 25, F= 25) with mean age of 2.4 years (SD 0.82) were evaluated. Anthropometry, Food Frequency Questionnaire, a hemogram and ferritin were measured. Twenty mg of elemental iron was given to all toddlers. After 8 weeks clinical examination, anthropometry, hemoglobin (HGB) and Ferritin were measured. RESULTS: Prevalence of anemia was 66% (HGB <11 gm %) and ferritin (iron stores) were low (< 12 microgm/L) in 45 (90%). After therapy prevalence of anemia was 30%. There was a significant difference in the HGB and ferritin levels of children after eight weeks of therapy ($p<0.001$). CONCLUSION: The prevalence of anemia decreased from 66 to 30% after treatment with liquid iron. We propose that all concerned in the care of toddlers should join the fight against anemia and prescribe iron to all toddlers when they are seen for minor ailments.

PMID: 18536890 [PubMed - indexed for MEDLINE]

Med Hypotheses. 2008;70(1):70-2. Epub 2007 Jun 18.

Iron deficiency anaemia influences cognitive functions.

Petranovic D, **Batinac T**, **Petranovic D**, **Ruzic A**, **Ruzic T**.

Department of Hematology, Rijeka University Hospital, Kresimirova 42, 51000 Rijeka, Croatia.

Many diseases, different nutritional, metabolic and hormonal changes, ageing and drugs can alter cognitive functions. Anemia via cerebral hypoxia and other possible mechanisms has been suggested to have a great influence on cognition. Iron deficiency anemia, the most common form of anemia, has been suggested to result in cognitive deterioration and alteration of neurological functions. Previous studies resulted in significant discrepancies considering correlation between anemia and cognitive achievement mainly because different or not sensitive enough tests used to measure cognition. We suggest a significant influence of iron deficiency anemia on dynamic properties and functional features of the central nervous system activity. Cognitive achievement is strongly related to hemoglobin level and could be expected in all patients. Higher hemoglobin level results in better CNS function. As a first step in confirming or refuting our hypotheses we suggest standardization of the method used to measure cognition, such as a very sensitive apparatus like Complex reactiometer Drenovac (CRD).

PMID: 17574345 [PubMed - indexed for MEDLINE]

Zhonghua Yu Fang Yi Xue Za Zhi. 2008 May;42(5):339-41.

[Anemia status and correlation factors in rural regions of Hebei province]

[Article in Chinese]

Wang YJ, **Li JG**, **Xu WL**, **Wang XB**, **Liu YL**, **Jiang H**.

Center for Disease Prevention and Control of Hebei Province, Shijiazhuang, China.

OBJECTIVE: To investigate anemia status and correlation infection factors in rural regions of Hebei province and to find out evidence for preventing and controlling anemia. METHODS: A random-sampling survey was conducted among 3367 houses in Hebei rural areas. The investigation involved economic levels, ages, education levels and occupations of 11,627 questionnaire. The hemoprotein and serum iron were measured. Unconditional logistic regression was performed. RESULTS: The anemia prevalence rate was shown up to 8.4% in rural regions of Hebei province, and in men and women was 5.5% and 11.0%, respectively;mainly in infant (< 2 years old, 27.2%) child bearing age women, the anemia prevalence rate was 11.0%-16.0%. The analysis showed that the main risk factors of anemia were sex and serum iron. CONCLUSION: The anemia prevalence is highest in infant and child bearing age women;supplying of iron should be an important measure for preventing and controlling anemia.

Publication Types:

- English Abstract

PMID: 18844084 [PubMed - indexed for MEDLINE]

Acta Chir Iugosl. 2007;54(1):91-105.

[Iron deficiency anemia and its importance in gastroenterology clinical practise]

[Article in Serbian]

Vucelić D, **Nenadić B**, **Pesko P**, **Bjelović M**, **Stojakov D**, **Sabljak P**, **Ebrahimi K**, **Dunjić S**, **Velicković D**, **Spica B**.

Klinika za digestivnu hirurgiju, Institut za bolesti digestivnog sistema, KCS, Beograd.

Iron deficiency anemia (IDA) is a universal problem involving individuals of all ages and both sexes and is a common cause of referral to medical departments. This anemia is one of the most common types of anemia. IDA impairs growth and intellectual development in children and adolescent. In women IDA is most common in reproductive period because of menstrual and pregnancy iron losses. IDA affects roughly 10-30% of all pregnancies and, among others morbidities, may contribute of developing postpartum depression. Among other adult patient, chronic occult gastrointestinal bleeding is the leading cause of IDA. Approximately, one third of patients with anemia have iron deficiency and up to two thirds of patients with IDA have serious gastrointestinal lesions detected with esophagogastroduodenoscopy and colonoscopy, including 10-15% with malignancy. However, in practice not all anemic patients undergo appropriate diagnostic tests to detect iron deficiency. Furthermore, a substantial proportion of patients with IDA do not undergo endoscopic evaluation. The approach to its investigation and subsequent therapy depends upon a comprehensive understanding of iron metabolism and heme synthesis. Once diagnosis of iron deficiency or IDA is established, evaluation for the cause of anemia must be appropriate performed and treatment must include corrective replenishment of body stores.

Publication Types:

- English Abstract
- Review

PMID: 17633868 [PubMed - indexed for MEDLINE]

J Health Popul Nutr. 2007 Mar;25(1):75-81.

Nutritional factors associated with anaemia in pregnant women in northern Nigeria.

Vanderjagt DJ, **Brock HS**, **Melah GS**, **El-Nafaty AU**, **Crossey MJ**, **Glew RH**.

Department of Biochemistry and Molecular Biology, University of New Mexico School of Medicine, Health Sciences Center, 1 University of New Mexico, Albuquerque, NM 87131-0001, USA.

This study was conducted to assess the relative contribution of iron, folate, and B 12 deficiency to anaemia in pregnant women in sub-Saharan Africa. In total, 146 pregnant women, who attended two antenatal clinics in Gombe, Nigeria, were recruited into the study. The majority (54%) of the women were in the third trimester. Blood samples were obtained for determination of haematocrit and for measurement of serum iron, total iron-binding capacity, ferritin, folate, vitamin B12, and homocysteine. Malaria was present in 15 (9.4%) women. Based on a haemoglobin value of<105 g/L, 44 (30%) women were classified as anaemic. The major contributing factor to anaemia was iron deficiency based on the serum concentration of ferritin (<10 ng/mL). The mean homocysteine concentration for all subjects was 14.1 pmol/L, and homocysteine concentrations were inversely correlated with concentrations of folate and vitamin B 12. The serum homocysteine increased markedly at serum vitamin B12 levels below 250 pmol/L. The most common cause of anaemia in the pregnant women in northern Nigeria was iron deficiency, and the elevated concentrations of homocysteine were most likely due to both their marginal folate and vitamin B12 status.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 17615906 [PubMed - indexed for MEDLINE]

Clin Drug Investig. 2005;25(11):679-89.

Overview of clinical trials in the treatment of iron deficiency with iron-acetyl-aspartylated casein.

Lazzari F, **Carrara M**.

General Medicine, Spedali Civili di Brescia, Distretto di Gardone VT, Brescia, Italy.

Iron therapy is necessary in a wide variety of clinical situations, and new formulations with improved tolerability and efficacy would be a welcome alternative to ferrous sulfate. A trivalent iron protein complex has been developed using an N-acetyl-aspartylated derivative of casein (Fe-ASP) for oral iron therapy. This paper provides an overview of the pharmacokinetic and clinical data on Fe-ASP use. To date, 704 paediatric and adult patients affected by iron deficiency anaemia with a wide variety of clinical histories (dietary, iron absorption defects, pregnancy, chronic or acute gastrointestinal haemorrhage) have been treated with Fe-ASP in 16 clinical trials including nine open and seven controlled trials. In healthy volunteers, Fe-ASP proved to be an efficient vehicle for providing iron with high bioavailability and more rapid and persistent increases in serum iron levels than ferritin. In open clinical trials, highly significant improvements in clinical and haematological parameters were observed after treatment with Fe-ASP in all categories of patients with iron deficiency anaemia. In controlled clinical trials, the changes in clinical and haematological profiles observed with Fe-ASP were virtually identical to those seen with iron protein succinylate (IPS), and Fe-ASP also compared well with parenteral iron gluconate. No safety considerations were raised.Fe-ASP shows high efficacy in iron-deficient anaemia treatment, and it is an extremely well tolerated iron vehicle. Fe-ASP represents a valid alternative to IPS and shows promise as a substitute for parenteral iron therapy in selected clinical situations.

PMID: 17532714 [PubMed - in process]

Transfus Clin Biol. 2007 May;14(1):21-4. Epub 2007 May 11.

[Iron deficiency anaemia: clinical presentation, biological diagnosis and management]

[Article in French]

Espanel C, **Kafando E**, **Hérault B**, **Petit A**, **Herault O**, **Binet C**.

Service d'hématologie, hôpital Bretonneau, CHRU de Tours, 2 boulevard Tonnellé, 37044 Tours cedex 9, France. espanel@med.univ-tours.fr

The iron deficiency is the first cause of anaemia. In healthy young adult, anemia is well tolerated because of its progressive installation. The most common symptoms of anemia are pallor, fatigue and dyspnea. In biological exams, anemia is classically associated with microcytosis and hypochromia. The origins of microcytic anemia are iron deficiency, inflammatory aetiologies, thalassemia and sideroblastic anaemia. The iron-deficiency diagnosis includes two explorations: biological and clinical. The biological exploration is based on interpretation of serum biologics tests as blood iron, ferritin, transferrin with saturation, total iron-binding capacity and its soluble receptors. This interpretation is simple if it is not associated with clinical disorders influencing the internal iron cycle. The clinical exploration must always be followed by a careful assessment of the underlying cause as blood loss. The most common causes in women of reproductive age are gynaecologic. In men and menopausal women, the gastrointestinal tract bleeding is source of anemia. Therapeutic management of anemia is oral iron therapy. Etiological diagnostic of microcytosis is essential before iron therapy. If not, the treatment could be inefficient or it could mask or delay the etiological diagnostic.

Publication Types:

- English Abstract

PMID: 17499537 [PubMed - indexed for MEDLINE]

Pol Merkur Lekarski. 2007 Jan;22(127):25-7.

[Concentration of ferritin, transferrin and iron as a markers of iron deficiency in healthy women in reproductive age]

[Article in Polish]

Chełchowska M, **Laskowska-Klita T**, **Leibschang J**.

Department of Biochemistry and Clinical Diagnostics, Institute of Mother and Child, Poland. lipidy@imid.med.pl

Iron deficiency anemia in pregnancy continues to be a clinical problem, which contributes to maternal and fetal morbidity. Iron store deficiency leads to iron deficient erythropoiesis and to negative iron balance when the iron supply is insufficient to maintain normal concentration of hemoglobin. The aim of this study was aimed to establish concentration of ferritin, transferrin and iron as a markers of iron deficiency in healthy women in reproductive age came for control examination to Institute of Mother and Child in Warsaw. MATERIAL AND METHODS: In serum of 108 healthy, multiparas in age up to 40 years from urban agglomerations, middle-class non-pregnant women concentration of iron, ferritin, transferrin and transferrin saturation were determined by commercially available kits (Hoffman-La Roche, Switzerland). RESULTS: Mean concentration of iron, ferritin and transferrin were among normal values. Low level of iron (below 49 microg/dl) was observed in serum of 12%, this of ferritin (below 20 ng/ml) in 22% and of transferrin (below 252 mg/dl) in 15% of studied women. Transferrin saturation lower than 15% was observed in 9 patients. The obtained values were age dependent. The lowest values of total iron were observed in the youngest group I (below 25 years old) and were accompanied with ferritin level below 20 ng/ml in 26% of women. Low ferritin values were also observed in serum of 22% patients of group II (25-35 years old) and only in 14% of women older than 35 years (group III). Saturation of transferrin lower than 15%, which indicated deficiency of iron for erythropoiesis, was observed in 26%, 13% and 19% patients of group I, II and III respectively. CONCLUSIONS: Obtained results indicated that in population of studied women in reproductive age, subclinical iron deficiency in 20% and negative iron balance in 10% could be observed. Therefore, iron status, especially store ferritin, should be assessed very carefully as a component of medical care.

PMID: 17477085 [PubMed - indexed for MEDLINE]

Int J Obes (Lond). 2007 Sep;31(9):1412-9. Epub 2007 Apr 17.

Inflammation and iron deficiency in the hypoferremia of obesity.

Yanoff LB, **Menzie CM**, **Denkinger B**, **Sebring NG**, **McHugh T**, **Remaley AT**, **Yanovski JA**.

Unit on Growth and Obesity, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, Bethesda, MD, USA.

CONTEXT: Obesity is associated with hypoferremia, but it is unclear if this condition is caused by insufficient iron stores or diminished iron availability related to inflammation-induced iron sequestration. OBJECTIVE: To examine the relationships between obesity, serum iron, measures of iron intake, iron stores and inflammation. We hypothesized that both inflammation-induced sequestration of iron and true iron deficiency were involved in the hypoferremia of obesity. DESIGN: Cross-sectional analysis of factors anticipated to affect serum iron. SETTING: Outpatient clinic visits. PATIENTS: Convenience sample of 234 obese and 172 non-obese adults. MAIN OUTCOME MEASURES: Relationships between serum iron, adiposity, and serum transferrin receptor, C-reactive protein, ferritin, and iron intake analyzed by analysis of covariance and multiple linear regression. RESULTS: Serum iron was lower (75.8+/-35.2 vs 86.5+/-34.2 g/dl, P=0.002), whereas transferrin receptor (22.6+/-7.1 vs 21.0+/-7.2 nmol/l, P=0.026), C-reactive protein (0.75+/-0.67 vs 0.34+/-0.67 mg/dl, P<0.0001) and ferritin (81.1+/-88.8 vs 57.6+/-88.7 microg/l, P=0.009) were higher in obese than non-obese subjects. Obese subjects had a higher prevalence of iron deficiency defined by serum iron (24.3%, confidence intervals (CI) 19.3-30.2 vs 15.7%, CI 11.0-21.9%, P=0.03) and transferrin receptor (26.9%, CI 21.6-33.0 vs 15.7%, CI 11.0-21.9%, P=0.0078) but not by ferritin (9.8%, CI 6.6-14.4 vs 9.3%, CI 5.7-14.7%, P=0.99). Transferrin receptor, ferritin and C-reactive protein contributed independently as predictors of serum iron. CONCLUSIONS: The hypoferremia of obesity appears to be explained both by true iron deficiency and by inflammatory-mediated functional iron deficiency.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 17438557 [PubMed - indexed for MEDLINE]

PMCID: PMC2266872

Ann Dermatol Venereol. 2007 Jan;134(1):45-7.

[Vulvar dermatitis and iron deficiency]

[Article in French]

Mateus C, **Franck N**, **Leclerc S**, **Brudy-Gulphe L**, **Plantier F**, **Dupin N**.

Service de Dermatologie, Institut Gustave Roussy, Villejuif.
christine.mateus@igr.fr

BACKGROUND: Many mucocutaneous signs associated with iron deficiency are described in the current dermatologic and haematologic literature but genital mucosa involvement has never been reported. CASE REPORT: We report a case of iron deficiency anaemia revealed by psoriasis-like vulvar dermatitis. The vulvar involvement dramatically improved after iron therapy. In the case reported herein, iron deficiency resulted from three mechanisms: increased loss (menorrhagia), inadequate dietary iron intake (vegetarian diet) and inadequate absorption (iron absorption inhibitors such as tea). DISCUSSION: Iron deficiency may be responsible for genital mucosa involvement. Iron deficiency investigation must determine the presence of blood loss and dietary habits (assessment of iron levels and ingestion of iron absorption inhibitors). Certain dietary recommendations are essential to avoid the failure of iron supplementation.

Publication Types:

- Case Reports
- English Abstract

PMID: 17384542 [PubMed - indexed for MEDLINE]

Am Fam Physician. 2007 Mar 1;75(5):671-8.

Erratum in:

- Am Fam Physician. 2008 Oct 15;78(8):914.

Iron deficiency anemia.

Killip S, **Bennett JM**, **Chambers MD**.

Department of Family and Community Medicine, University of Kentucky, Lexington, Kentucky, USA.

The prevalence of iron deficiency anemia is 2 percent in adult men, 9 to 12 percent in non-Hispanic white women, and nearly 20 percent in black and Mexican-American women. Nine percent of patients older than 65 years with iron deficiency anemia have a gastrointestinal cancer when evaluated. The U.S. Preventive Services Task Force currently recommends screening for iron deficiency anemia in pregnant women but not in other groups. Routine iron supplementation is recommended for high-risk infants six to 12 months of age. Iron deficiency anemia is classically described as a microcytic anemia. The differential diagnosis includes thalassemia, sideroblastic anemias, some types of anemia of chronic disease, and lead poisoning. Serum ferritin is the preferred initial diagnostic test. Total iron-binding capacity, transferrin saturation, serum iron, and serum transferrin receptor levels may be helpful if the ferritin level is between 46 and 99 ng per mL (46 and 99 mcg per L); bone marrow biopsy may be necessary in these patients for a definitive diagnosis. In children, adolescents, and women of reproductive age, a trial of iron is a reasonable approach if the review of symptoms, history, and physical examination are negative; however, the hemoglobin should be checked at one month. If there is not a 1 to 2 g per dL (10 to 20 g per L) increase in the hemoglobin level in that time, possibilities include malabsorption of oral iron, continued bleeding, or unknown lesion. For other patients, an endoscopic evaluation is recommended beginning with colonoscopy if the patient is older than 50.

Publication Types:

- Review

PMID: 17375513 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2007 Mar;85(3):778-87.

Iron treatment normalizes cognitive functioning in young women.

Murray-Kolb LE, **Beard JL**.

Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA. lmurrayk@jhsph.edu

BACKGROUND: Evidence suggests that brain iron deficiency at any time in life may disrupt metabolic processes and subsequently change cognitive and behavioral functioning. Women of reproductive age are among those most vulnerable to iron deficiency and may be at high risk for cognitive alterations due to iron deficiency. OBJECTIVE: We aimed to examine the relation between iron status and cognitive abilities in young women. DESIGN: A blinded, placebo-controlled, stratified intervention study was conducted in women aged 18-35 y of varied iron status who were randomly assigned to receive iron supplements or a placebo. Cognition was assessed by using 8 cognitive performance tasks (from Detterman's Cognitive Abilities Test) at baseline (n = 149) and after 16 wk of treatment (n = 113). RESULTS: At baseline, the iron-sufficient women (n = 42) performed better on cognitive tasks (P = 0.011) and completed them faster (P = 0.038) than did the women with iron deficiency anemia (n = 34). Factors representing performance accuracy and the time needed to complete the tasks by the iron-deficient but nonanemic women (n = 73) were intermediate between the 2 extremes of iron status. After treatment, a significant improvement in serum ferritin was associated with a 5-7-fold improvement in cognitive performance, whereas a significant improvement in hemoglobin was related to improved speed in completing the cognitive tasks. CONCLUSIONS: Iron status is a significant factor in cognitive performance in women of reproductive age. Severity of anemia primarily affects processing speed, and severity of iron deficiency affects accuracy of cognitive function over a broad range of tasks. Thus, the effects of iron deficiency on cognition are not limited to the developing brain.

Publication Types:

- Randomized Controlled Trial
- Research Support, N.I.H., Extramural
- Research Support, U.S. Gov't, Non-P.H.S.

PMID: 17344500 [PubMed - indexed for MEDLINE]

J Clin Gastroenterol. 2007 Jan;41(1):41-4.

Iron-deficiency anemia as presentation of pouchitis.

Pastrana RJ, **Torres EA**, **Arroyo JM**, **Rivera CE**, **Sánchez CJ**, **Morales L**.

Gastroenterology Research Unit, Department of Medicine, University of Puerto Rico School of Medicine, University of Puerto Rico, San Juan, PR.

GOALS: This study sought to describe the percentage and cause of anemia in patients who underwent ileal pouch with anal anastomosis (IPAA) for ulcerative colitis (UC), and to compare the distribution of complications in patients with and without anemia, especially pouchitis, after IPAA. BACKGROUND: IPAA is the surgical procedure of choice for UC. Complications include pouchitis (40%), strictures (30%), small bowel obstruction (10%), pelvic sepsis (<5%), and urinary and sexual dysfunctions (<5%). Few studies have described the prevalence of anemia after IPAA, but no conclusive findings have been reported. STUDY: Patients who had undergone IPAA for UC were recruited from the UPR Inflammatory Bowel Disease Clinic and the Gastroenterology Research Unit. Demographic and medical data were obtained. Anemia was diagnosed using standard hematologic criteria. Serum iron, ferritin, transferrin, folate, vitamin B12, erythropoietin, total iron-binding capacity, reticulocyte count, peripheral smear, and bone marrow aspirate were evaluated in patients with anemia. Data analysis was performed with EPI Info version 6.4d. RESULTS: Iron-deficiency anemia was identified in 55.5% (10/18) of patients and pouchitis was found in 77% (14/18). All 10 patients with anemia had pouchitis, whereas only 4 of the 8 without anemia had pouchitis. In half of the anemic patients, pouchitis was asymptomatic. CONCLUSIONS: Iron-deficiency anemia may be a clinical presenting sign of pouchitis. Hemoglobin levels may be considered as surveillance tools for pouchitis in patients with IPAA.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 17198064 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2009 Mar;89(3):853-61. Epub 2009 Jan 28.

Treatment response to standard of care for severe anemia in pregnant women and effect of multivitamins and enhanced anthelminthics.

Christian P, **Shahid F**, **Rizvi A**, **Klemm RD**, **Bhutta ZA**.

Center for Human Nutrition, Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD 21205, USA. pchristi@jhsph.edu

BACKGROUND: Severe anemia (hemoglobin < 70 g/L) in pregnancy may increase the risk of maternal and perinatal mortality. OBJECTIVES: We assessed response to standard treatment with high-dose iron-folic acid for 90 d and single-dose (500 mg) mebendazole among severely anemic pregnant women in periurban Karachi, Pakistan. In addition, we evaluated the efficacy of 2 enhanced treatment regimens. DESIGN: We screened pregnant women (n = 6288) for severe anemia and provided them all with the standard treatment. To test the efficacy of 2 additional treatments, women were randomly assigned to standard treatment alone (control) or with 100 mg mebendazole twice daily for 3 d or 90 d of daily multivitamins or both using a 2 x 2 factorial design. RESULTS: Prevalence of severe anemia was high (10.5%) during pregnancy. Prevalence of geohelminths and malaria was low. Treatment response was defined as hemoglobin > 100 g/L at the 90-d or > or = 25 g/L at the 60-d follow-up visit. The standard-of-care treatment resulted in a response rate of 49% at follow-up, although an adherence of > or = 85% elicited a higher response (67%). The effect of the additional treatments was weak. Although response was higher in the enhanced groups than for the standard treatment at the final assessment, the differences were not statistically significant. However, hemoglobin concentration increased significantly in all groups and was higher in the enhanced mebendazole group compared with the standard group (P < 0.05). CONCLUSIONS: Iron deficiency was high in this population, and the standard-of-care treatment resulted in a treatment response of 50%, although better treatment adherence showed a higher response. Multivitamins and the enhanced mebendazole regimen had a modest benefit over and above the standard treatment.

Publication Types:

- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 19176737 [PubMed - indexed for MEDLINE]

Iron and Blood Improvement

Nagoya J Med Sci. 2009 Feb;71(1-2):39-49.

Iron and iodine deficiencies among under-2 children, adolescent girls, and pregnant women of Bangladesh: association with common diseases.

Harun-Or-Rashid M, **Khatun UF**, **Yoshida Y**, **Morita S**, **Chowdhury N**, **Sakamoto J**.

Department of Healthcare Administration, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan. mh_rashid67@yahoo.com

We examined the frequency of iron and iodine deficiencies and associations of iron and iodine deficiencies with common diseases among under-2 children, adolescent girls, and pregnant women of Bangladesh. We assayed the blood hemoglobin concentration in 395 under-2 children, 355 adolescent girls, and 263 pregnant women, the urinary iodine concentration of those adolescent girls and pregnant women, and the iodine level of all household salt specimens. The history of common diseases within their previous 2 weeks were also obtained from recall to explore the associations of iron and iodine deficiencies with common diseases. Anemia was found in 49.1% of children, 24.8% of adolescent girls, and 44.4% of pregnant women using defined cut-off values (Hb < 11.0 g/dL for under-2 children and pregnant women; <12.0 g/dL for adolescent girls). Prevalence of iodine deficiencies (urinary iodine <100 microg/L) was 38.4% in adolescent girls and 39.4% in pregnant women, and 39.4% of salt specimens had inadequate iodine (<15 ppm). The relative risk (RR) and 95% confidence intervals (CI) were estimated and adjusted for age, sex, and gestational age to explore the associations of iron and iodine deficiencies with common diseases. The RR of anemia was increased for fever (RR = 1.7, 95% CI = 1.3-2.3), ear infection (RR = 3.4, 95% CI = 1.3-8.5), skin disease (RR = 1.4, 95% CI = 0.9-2.2), and pneumonia (RR = 3.7, 95% CI = 0.7-19.5). The RR of iodine deficiency was elevated for diarrhea/dysentery (RR = 2.2, 95% CI = 1.1l-4.4) and eye infection (RR = 2.1, 95% CI = 0.5-9.4). We concluded that iron and iodine deficiencies are quite high among the Bangladeshi population. Observed associations of iron and iodine deficiencies with common diseases indicated the necessity of eliminating iron and iodine deficiencies from this vulnerable population through strengthening of iron and iodine supplementation, in order to prevent diseases and promote health conditions.

PMID: 19358474 [PubMed - indexed for MEDLINE]

Free Radic Res. 2008 Sep;42(9):824-9.

Iron-deficiency anaemia enhances red blood cell oxidative stress.

Nagababu E, **Gulyani S**, **Earley CJ**, **Cutler RG**, **Mattson MP**, **Rifkind JM**.

Molecular Dynamics Section, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA.

Oxidative stress associated with iron deficiency anaemia in a murine model was studied feeding an iron-deficient diet. Anaemia was monitored by a decrease in hematocrit and haemoglobin. For the 9 week study an increase in total iron binding capacity was also demonstrated. Anaemia resulted in an increase in red blood cells (RBC) oxidative stress as indicated by increased levels of fluorescent heme degradation products (1.24-fold after 5 weeks; 2.1-fold after 9 weeks). The increase in oxidative stress was further confirmed by elevated levels of methemoglobin for mice fed an iron-deficient diet. Increased haemoglobin autoxidation and subsequent generation of ROS can account for the shorter RBC lifespan and other pathological changes associated with iron-deficiency anaemia.

PMID: 19051108 [PubMed - indexed for MEDLINE]

Zhonghua Yu Fang Yi Xue Za Zhi. 2008 Jun;42(6):437-41.

[Effect of NaFeEDTA on serum ferritin level in iron deficient epidemic population: a systematic review]

[Article in Chinese]

Wang B, **Zhan SY**, **Xia YY**, **Li LM**.

Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Key Laboratory of Epidemiology, Ministry of Education, Beijing 100083, China.

OBJECTIVE: To evaluate effect of NaFeEDTA on serum ferritin level in iron deficient epidemic population. METHODS: A comprehensive literature retrieval was performed via searching electronic databases, hand searching bibliographies of books and relevant journals, collecting grey literatures, looking into conference abstracts, contacting fields experts and reviewing references and citations. Criteria from Cochrane EPOC review group were used to assess the quality of the included studies. Generic inverse variance method was used to undertake Meta-analysis. RESULTS: The pooled estimate for serum ferritin level (weighted mean difference) was 1.58 microg/L (95% CI 1.20-2.09; $P < 0.001$). CONCLUSION: This systematic review indicates that NaFeEDTA might improve serum ferritin concentration significantly in iron deficient epidemic population.

Publication Types:

- English Abstract
- Meta-Analysis
- Review

PMID: 19035048 [PubMed - indexed for MEDLINE]

Am J Med. 2008 Nov;121(11):943-8.

Individualized treatment for iron-deficiency anemia in adults.

Alleyne M, **Horne MK**, **Miller JL**.

The National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-1801, USA.

Iron deficiency is one of the most common disorders affecting humans, and iron-deficiency anemia continues to represent a major public health problem worldwide. It is especially common among women of childbearing age because of pregnancy and menstrual blood loss. Additional patient groups include those with other sources of blood loss, malnutrition, or gut malabsorption. Iron-deficiency anemia remains prevalent despite the widespread ability to diagnose the disease and availability of medicinal iron preparations. Therefore, new approaches are needed to effectively manage these patient populations. In this review, the diagnosis and treatment of iron-deficiency anemia are discussed with emphasis placed on consideration of patient-specific features. It is proposed that all patients participate in their own care by helping their physician to identify a tolerable daily iron dose, formulation, and schedule. Dosing cycles are recommended for iron replacement based on the tolerated daily dose and the total iron deficit. Each cycle consists of 5000 mg of oral elemental iron ingested over at least 1 month with appropriate follow-up. This approach should assist physicians and their patients with the implementation of individualized treatment strategies for patients with iron-deficiency anemia.

Publication Types:

- Research Support, N.I.H., Intramural
- Review

PMID: 18954837 [PubMed - indexed for MEDLINE]

PMCID: PMC2582401 [Available on 2009/11/01]

Food Nutr Bull. 2008 Sep;29(3):186-94.

Weekly iron and folic acid supplementation with counseling reduces anemia in adolescent girls: a large-scale effectiveness study in Uttar Pradesh, India.

Vir SC, **Singh N**, **Nigam AK**, **Jain R**.

Public Health Nutrition and Development Centre, New Delhi.
sheila.vir@gmail.com

BACKGROUND: Weekly iron-folic acid supplementation in small-scale research trials and as administered in institutions has been demonstrated to be effective in reducing anemia in adolescent girls. OBJECTIVE: To assess the effectiveness of weekly iron-folic acid supplementation in a large-scale project in reducing the prevalence of anemia in adolescent girls. METHODS: The project provided weekly iron-folic acid tablets, family life education, and deworming tablets every 6 months to 150,700 adolescent school girls and non-schoolgirls of a total district population of 3,647,834. Consumption of the iron-folic acid tablets was supervised for schoolgirls but not for non-schoolgirls. Hemoglobin levels were assessed in a random sample of non-schoolgirls at 6 and 12 months and schoolgirls at 6 months. The effect of supplementation on the prevalence of anemia and the compliance rate were assessed over a 4-year period. RESULTS: In 4 years, the overall prevalence of anemia was reduced from 73.3% to 25.4%. Hemoglobin levels and anemia prevalence were influenced significantly at 6 months. No difference in the impact on hemoglobin or anemia prevalence was observed between supervised and unsupervised girls. Counseling on the positive effects of regular weekly iron-folic acid intake contributed to a high compliance rate of over 85%. The cost of implementation was US$0.36 per beneficiary per year. CONCLUSIONS: Weekly iron-folic acid supplementation combined with monthly education sessions and deworming every 6 months is cost-effective in reducing the prevalence of anemia in adolescent girls. Appropriate counseling, irrespective of supervision, is critical for achieving positive outcomes.

PMID: 18947031 [PubMed - indexed for MEDLINE]

Nutrition. 2008 Nov-Dec;24(11-12):1116-22. Epub 2008 Aug 9.

Anemia, nutritional status, and inflammation in hospitalized elderly.

Ramel A, **Jonsson PV**, **Bjornsson S**, **Thorsdottir I**.

Unit for Nutrition Research, Landspitali-University Hospital, and Department of Food Science and Human Nutrition, University of Iceland, Reykjavik, Iceland. alfons@landspitali.is

OBJECTIVE: Anemia (hemoglobin <120 g/L) in elderly patients is a health problem. The aim of this study was to investigate the prevalence of anemia and associations of anemia with nutritional status and inflammation in hospitalized elderly. METHODS: Sixty patients from the Department of Geriatrics were randomly assigned to participate. Blood samples were drawn and analyzed at the laboratory of the University Hospital in Reykjavik. Nutritional status was assessed using anthropometric and hematologic parameters. RESULTS: The prevalence of anemia was 36.7%. Female participants were more frequently anemic than male participants (47.4% versus 18.2%, P = 0.024). Anemic patients had a lower albumin level (31.3 versus 33.4 g/L, P = 0.019) and a higher erythrocyte sedimentation rate (29.6 versus 16.0 mm/h, P = 0.005) and were more often malnourished (81.8% versus 44.7%, P = 0.005) than non-anemic patients. Hemoglobin correlated with prealbumin (rho = 0.338, P = 0.008) and albumin (rho = 0.250, P = 0.054) levels, but negatively with age (rho = -0.310, P = 0.016) and erythrocyte sedimentation rate (rho = -0.412, P < 0.001). In the multivariate analysis, erythrocyte sedimentation rate and nutritional status were significant predictors of hemoglobin (R(2) = 34.0%). CONCLUSION: This cross-sectional analysis provides evidence of anemia in 36.7% of patients hospitalized at the Landspitali-University Hospital in Reykjavik and shows an association among anemia, deteriorated nutritional status, and inflammation. Future prospective studies are needed to assess the efficacy of adjuvant nutritional support to stabilize or improve nutritional status including anemia in hospitalized elderly.

PMID: 18692363 [PubMed - indexed for MEDLINE]

Nutr Cancer. 2008;60(4):474-82.

Blood iron, glutathione, and micronutrient levels and the risk of oral cancer.

Richie JP Jr, **Kleinman W**, **Marina P**, **Abraham P**, **Wynder EL**, **Muscat JE**.

Department of Public Health Sciences, Penn State Cancer Institute, Penn State University College of Medicine, Hershey, Pennsylvania 17033, USA. jrichie@psu.edu

The risk of oral cavity cancer was determined in relation to serological levels of iron; vitamins A, B2, C, E; zinc; thiamin; and glutathione (GSH). The study included 65 hospitalized patients with oral cancer and 85 matched controls. In comparing the highest to the lowest tertiles, the risk was odds ratio (OR) = 0.3 [95% confidence interval (CI) = 0.1-0.6] for iron; 3.2 (95% CI = 1.3-8.1) for total iron binding capacity (TIBC), which measures the concentration of the iron delivery protein transferrin; and 0.4 (95% CI = 0.2-0.9) for transferrin saturation (iron/TIBC x 100). These associations were stronger in never smokers than in ever smokers. The risk associated with the iron storage protein ferritin was significantly elevated, but this association could reflect disease-related inflammation or comorbidity. The OR for GSH was 0.4 (95% CI = 0.1-0.9), and the OR for GSH reductase activity coefficient (indicative of riboflavin deficiency) was 1.6 (95% CI = 1.3-3.7). These findings suggest that mild iron deficiency and low GSH levels, which are associated with increased oxidative stress, increase the risk of oral cavity cancer.

Publication Types:

- Research Support, N.I.H., Extramural

PMID: 18584481 [PubMed - indexed for MEDLINE]

Eur J Clin Nutr. 2008 Aug;62(8):946-52. Epub 2007 May 23.

Prenatal iron supplementation in rural Vietnam.

Aikawa R, **Jimba M**, **Nguen KC**, **Binns CW**.

School of Public Health, Curtin University of Technology, Perth, Australia.

OBJECTIVE: To assess the potential impact of a national iron supplementation programme in rural Vietnam. METHODS: The study included questionnaires, focus group discussions of pregnant women and key informant interviews, together with measurements of haemoglobin (Hb) and a stool examination for soil-transmitted helminths. RESULTS: Iron supplementation significantly increased Hb concentration among participants in the second and third trimesters by 0.4 and 0.7 g/dl, respectively (P=0.017 and P<0.001). The risk of anaemia (Hb <10.0 g/dl) was increased significantly by hookworm infestation (P=0.041) and in summer season (P=0.001) and was decreased significantly by taking iron tablets (P=0.041). CONCLUSIONS: The results of this study show that an iron supplementation programme is beneficial as a part of a comprehensive anaemia programme for pregnant women in these communities. These results will be useful for developing improved iron-deficiency anaemia control programs for pregnant women.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17522600 [PubMed - indexed for MEDLINE]

J Pediatr (Rio J). 2007 Mar-Apr;83(2):149-56.

Risk factors for anemia in infants assisted by public health services: the importance of feeding practices and iron supplementation.

Silva DG, **Priore SE**, **Franceschini Sdo C**.

Universidade Federal de Viçosa, Viçosa, MG, Brasil.

OBJECTIVE: To investigate risk factors for anemia in infants assisted by public health services. METHODS: In a cross-sectional study carried out in Viçosa, state of Minas Gerais, Brazil, 205 children from 6 to 12 months were evaluated. Socioeconomic, environmental and biological data were collected, as well as information on child's birth, nutritional status, maternal data, child health care practices, feeding practices, and iron supplementation. Diagnosis of anemia was based on hemoglobin levels under 11 g/dL, using a portable Hemocue photometer. To analyze variables associated with anemia, a hierarchical logistic regression model was used. RESULTS: The prevalence of anemia was 57.6%. Family income per capita less than 0.5 minimum wage, frequency of fruit intake less than daily and lack of iron supplementation increased the chance of anemia among infants. CONCLUSION: Adequate health and nutrition support to low income families, promotion of healthy nutritional habits and prescription of iron supplements are of great importance to prevent and manage anemia in infants assisted by public health services.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17426870 [PubMed - indexed for MEDLINE]

Toxicol Appl Pharmacol. 2007 Feb 15;219(1):33-41. Epub 2006 Dec 8.

Iron supplement prevents lead-induced disruption of the blood-brain barrier during rat development.

Wang Q, **Luo W**, **Zheng W**, **Liu Y**, **Xu H**, **Zheng G**, **Dai Z**, **Zhang W**, **Chen Y**, **Chen J**.

Department of Occupational and Environmental Health, Faculty of Military Preventive Medicine, Fourth Military Medical University, 17 Changlexi Street, Xi'an, 710032, China.

Children are known to be venerable to lead (Pb) toxicity. The blood-brain barrier (BBB) in immature brain is particularly vulnerable to Pb insults. This study was designed to test the hypothesis that Pb exposure damaged the integrity of the BBB in young animals and iron (Fe) supplement may prevent against Pb-induced BBB disruption. Male weanling Sprague-Dawley rats were divided into four groups. Three groups of rats were exposed to Pb in drinking water containing 342 microg Pb/mL as Pb acetate, among which two groups were concurrently administered by oral gavage once every other day with 7 mg Fe/kg and 14 mg Fe/kg as FeSO(4) solution as the low and high Fe treatment group, respectively, for 6 weeks. The control group received sodium acetate in drinking water. Pb exposure significantly increased Pb concentrations in blood by 6.6-folds ($p<0.05$) and brain tissues by 1.5-2.0-folds ($p<0.05$) as compared to controls. Under the electron microscope, Pb exposure in young animals caused an extensive extravascular staining of lanthanum nitrate in brain parenchyma, suggesting a leakage of cerebral vasculature. Western blot showed that Pb treatment led to 29-68% reduction ($p<0.05$) in the expression of occludin as compared to the controls. Fe supplement among Pb-exposed rats maintained the normal ultra-structure of the BBB and restored the expression of occludin to normal levels. Moreover, the low dose Fe supplement significantly reduced Pb levels in blood and brain tissues. These data suggest that Pb exposure disrupts the structure of the BBB in young animals. The increased BBB permeability may facilitate the accumulation of Pb. Fe supplement appears to protect the integrity of the BBB against Pb insults, a beneficial effect that may have significant clinical implications.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 17234227 [PubMed - indexed for MEDLINE]

Pak J Biol Sci. 2007 Jan 15;10(2):255-60.

Effect of iron repletion and correction of iron deficiency on thyroid function in iron-deficient Iranian adolescent girls.

Eftekhari MH, **Eshraghian MR**, **Mozaffari-Khosravi H**, **Saadat N**, **Shidfar F**.

Department of Nutrition, School of Health, Shiraz University of Medical Sciences, P.O. Box 71645-111, Shiraz, Islamic Republics of Iran.

The aim of this study was to determine whether iron supplementation in iron-deficient adolescent girls would improve thyroid function. A double-blind clinical trial was performed in a region in southern I.R. Iran. A total of 103 iron deficient participants were chosen. In all, 94 participants successfully completed this study. Participants were randomly assigned to one of two groups and treated with a 300 mg ferrous sulfate 5 times/week (n = 47) and placebo 5 times/week (n = 47) for 12 weeks. Blood samples were collected and assayed for hemoglobin, hematocrit, serum ferritin, iron, total iron binding capacity (TIBC), Thyroid stimulating hormone (TSH), total thyroxine (TT4), total triiodothyronine (TT3), free thyroid hormones (FT4 and FT3), triiodothyronine resin uptake (T3RU), reverse triiodothyronine (rT3), selenium and albumin concentrations. Statistical analysis was performed with parametric and non-parametric methods as appropriate. Data analysis revealed a significant increase in TT4, TT3, T3RU and a significant decrease in rT3 concentration in comparison to initial values in iron treated group (12%, $p<0.001$; 3.5%, $p<0.001$; 16%, $p<0.05$ and 47%, $p<0.001$, respectively). At 12 week there were significant differences between control and placebo in TT4, TT3, T3RU and rT3 concentrations (9.9 vs 8.4 microg dL(-1), 145.2 vs 130.4 microg dL(-1), 32.5 vs 28.4% and 23 vs 41 microg dL(-1), respectively, all $p<0.001$). Alterations in FT3 and TSH concentration were not significant, but concentration of FT4 revealed a significant difference between the beginning and the end of the study in iron treated group (10.3 vs 11.4, $p<0.001$). Iron supplementation improves some indices of thyroid function in iron-deficient adolescent girls.

Publication Types:

- Clinical Trial
- Comparative Study
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 19070025 [PubMed - indexed for MEDLINE]

Iron and Blood Improvement

Tex Heart Inst J. 2006;33(3):340-4.

The cardiomyopathy of iron deficiency.

Hegde N, **Rich MW**, **Gayomali C**.

Department of Medicine, Summa Health System and Northeastern Ohio Universities College of Medicine (NEOUCOM), Akron, Ohio 44304, USA.

Iron-deficiency anemia can have deleterious effects on the heart. Herein, we describe the effects of iron deficiency on the heart as corroborated with electrocardiography, radiology, echocardiography, and cardiac catheterization. We review the pathophysiology, clinical features, and management of iron-deficiency-induced cardiomyopathy.

Publication Types:

- Case Reports

PMID: 17041692 [PubMed - indexed for MEDLINE]

PMCID: PMC1592266

Hypertension. 2008 Jan;51(1):154-9. Epub 2007 Oct 29.

Long-term circulatory consequences of perinatal iron deficiency in male Wistar rats.

Bourque SL, **Komolova M**, **Nakatsu K**, **Adams MA**.

Department of Pharmacology and Toxicology, Faculty of Health Sciences, Queen's University, Kingston, Ontario, Canada K7L 3N6.

Perinatal iron deficiency (PID) has been reported to induce developmental abnormalities, including cardiovascular complications in rats. These complications are believed to be "programmed" by an aberrant perinatal environment because the changes persist long after the insult is corrected (ie, despite subsequent iron replenishment). Little is known about the mechanisms by which PID affects blood pressure in the offspring, although the kidney is likely to play a central role. The objective of this study was to investigate the circulatory complications of PID and the putative role of the kidney involved therein. Before and throughout gestation, female Wistar rats were fed either a low-iron diet (3 ppm/10 ppm Fe) or an iron-enriched diet (225 ppm Fe). After giving birth, all of the dams were placed on a standard grain-based diet. At 24 hours postpartum, hematocrits and hemoglobin levels from offspring of iron-deficient mothers were 60% and 59% of control values, respectively. Adult PID animals had greater mean arterial pressures (110 versus 106 mm Hg) and systolic blood pressures (129 versus124 mm Hg) than controls, as assessed by radiotelemetry. The relationship between renal arterial pressure and renal interstitial hydrostatic pressure, assessed in anesthetized rats, was blunted by 41% in the PID group compared with controls. In addition, arterial pressure changes were significantly greater in response to altered sodium in the PID animals compared with controls. These data confirm that PID adversely affects blood pressure control, which seems to be mediated, at least in part, by altered intrarenal hemodynamic properties.

PMID: 17967999 [PubMed - indexed for MEDLINE]

Am J Physiol Heart Circ Physiol. 2009 Mar;296(3):H585-93. Epub 2009 Jan 9.

Adaptive response of the heart to long-term anemia induced by iron deficiency.

Naito Y, **Tsujino T**, **Matsumoto M**, **Sakoda T**, **Ohyanagi M**, **Masuyama T**.

Cardiovascular Division, Dept. of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya 663-8501, Japan.

Anemia is common in patients with chronic heart failure and an independent predictor of poor prognosis. Chronic anemia leads to left ventricular (LV) hypertrophy and heart failure, but its molecular mechanisms remain largely unknown. We investigated the mechanisms, including the molecular signaling pathway, of cardiac remodeling induced by iron deficiency anemia (IDA). Weanling Sprague-Dawley rats were fed an iron-deficient diet for 20 wk to induce IDA, and the molecular mechanisms of cardiac remodeling were evaluated. The iron-deficient diet initially induced severe anemia, which resulted in LV hypertrophy and dilation with preserved systolic function associated with increased serum erythropoietin (Epo) concentration. Cardiac STAT3 phosphorylation and VEGF gene expression increased by 12 wk of IDA, causing angiogenesis in the heart. Thereafter, sustained IDA induced upregulation of cardiac hypoxia inducible factor-1alpha gene expression and maintained upregulation of cardiac VEGF gene expression and cardiac angiogenesis; however, sustained IDA promoted cardiac fibrosis and lung congestion, with decreased serum Epo concentration and cardiac STAT3 phosphorylation after 20 wk of IDA compared with 12 wk. Upregulation of serum Epo concentration and cardiac STAT3 phosphorylation is associated with a beneficial adaptive mechanism of anemia-induced cardiac hypertrophy, and later decreased levels of these molecules may be critical for the transition from adaptive cardiac hypertrophy to cardiac dysfunction in long-term anemia. Understanding the mechanism of cardiac maladaptation to anemia may lead to a new strategy for treatment of chronic heart failure with anemia.

J Neurochem. 2007 Dec;103(5):1730-40. Epub 2007 Oct 22.

Iron trafficking inside the brain.

Moos T, **Rosengren Nielsen T**, **Skjørringe T**, **Morgan EH**.

Department of Health Science and Technology, Aalborg University, Aalborg, Denmark. tmoos@hst.aau.dk

Iron, an essential element for all cells of the body, including those of the brain, is transported bound to transferrin in the blood and the general extracellular fluid of the body. The demonstration of transferrin receptors on brain capillary endothelial cells (BCECs) more than 20 years ago provided the evidence for the now accepted view that the first step in blood to brain transport of iron is receptor-mediated endocytosis of transferrin. Subsequent steps are less clear. However, recent investigations which form the basis of this review have shed some light on them and also indicate possible fruitful avenues for future research. They provide new evidence on how iron is released from transferrin on the abluminal surface of BCECs, including the role of astrocytes in this process, how iron is transported in brain extracellular fluid, and how iron is taken up by neurons and glial cells. We propose that the divalent metal transporter 1 is not involved in iron transport through the BCECs. Instead, iron is probably released from transferrin on the abluminal surface of these cells by the action of citrate and ATP that are released by astrocytes, which form a very close relationship with BCECs. Complexes of iron with citrate and ATP can then circulate in brain extracellular fluid and may be taken up in these low-molecular weight forms by all types of brain cells or be bound by transferrin and taken up by cells which express transferrin receptors. Some iron most likely also circulates bound to transferrin, as neurons contain both transferrin receptors and divalent metal transporter 1 and can take up transferrin-bound iron. The most likely source for transferrin in the brain interstitium derives from diffusion from the ventricles. Neurons express the iron exporting carrier, ferroportin, which probably allows them to excrete unneeded iron. Astrocytes lack transferrin receptors. Their source of iron is probably that released from transferrin on the abluminal surface of BCECs. They probably to export iron by a mechanism involving a membrane-bound form of the ferroxidase, ceruloplasmin. Oligodendrocytes also lack transferrin receptors. They probably take up non-transferrin bound iron that gets incorporated in newly synthesized transferrin, which may play an important role for intracellular iron transport.

PMID: 17953660 [PubMed - indexed for MEDLINE]

Int J Obes (Lond). 2008 Sep;32(9):1441-4. Epub 2008 Jul 8.

Sedentariness and increased visceral adiposity in adult perinatally iron-deficient rats.

Komolova M, **Bourque SL**, **Nakatsu K**, **Adams MA**.

Department of Pharmacology and Toxicology, Queen's University, Kingston, Ontario, Canada.

BACKGROUND: Perinatal iron deficiency (PID) adversely programs offspring resulting in alterations in adult cardiometabolic function. Increased visceral adiposity is the proposed culprit for these sequelae, and may be potentiated by decreased physical activity. Herein, we determined (i) the effect of PID on visceral adipose tissue (VAT) and locomotor activity, and (ii) whether increased VAT is associated with blood pressure responsiveness to increased dietary sodium. METHODS AND RESULTS: Dams were fed a low iron diet (<10 mg/kg Fe) prior to and throughout gestation. From 12 to 35 weeks of age, locomotor activity (assessed by radiotelemetry) in PID offspring was 25% lower compared with control offspring ($P<0.001$). At 36 weeks of age, PID offspring had 15% more VAT than controls ($P<0.05$). Furthermore, the elevation of mean arterial pressure (by radiotelemetry) in response to increased sodium intake was approximately twofold greater in the PID offspring ($P<0.05$). CONCLUSIONS: PID results in increased visceral adiposity, which was associated with enhanced blood pressure responsiveness to dietary salt, perhaps due to programmed sedentary behavior.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18607379 [PubMed - indexed for MEDLINE]

J Pediatr Hematol Oncol. 2007 Nov;29(11):747-51.

Do cerebral blood flow velocities change in iron deficiency anemia?

Aliefendioglu D, **Yilmaz S**, **Misirlioglu ED**, **Saygi S**, **Ozdogan S**, **Kocak U**.

Department of Pediatrics, School of Medicine, Kirikkale University, Kirikkale, Turkey. didem.aliefendioglu@gmail.com

Infants with iron deficiency had lower scores when tested for mental and motor development than their peers with better iron status. The aim of this study was to examine cerebral blood flow velocity in infants with iron deficiency anemia. Thirty-six infants (27 male, 9 female) with iron deficiency anemia, aged 6 to 36 months were divided into 2 groups according to the hemoglobin (Hb) values [group 1 (n=23) Hb<10 g/dL and group 2 (n=13) 11 >Hb> or =10 g/dL]. In anterior and middle cerebral arteries only end-diastolic velocity (EDV) was increased in group 1 as compared with group 2 (P=0.05 and P=0.016, respectively), whereas in posterior cerebral artery both EDV and peak-systolic velocity were different between the groups (P=0.024 and P=0.004). Both peak-systolic velocity and EDV showed significant correlation with Hb level in the posterior cerebral artery (r=-0.38, P=0.023 and r=-0.35, P=0.037) but not in the anterior and middle cerebral arteries. Increased cerebral blood flow velocities in children with lower Hb values may be due to increased cardiac output, decreased vascular resistivity caused by anemia.

PMID: 17984692 [PubMed - indexed for MEDLINE]

Vitamin B-12 and Brain Health

Prog Neurobiol. 2009 Apr 24. [Epub ahead of print]

The multi-faceted basis of vitamin B(12) (cobalamin) neurotrophism in adult central nervous system: Lessons learned from its deficiency.

Scalabrino G.

Institute of General Pathology, University of Milan, Via Mangiagalli 31, 20133 Milano, Italy.

Glial cells, myelin and the interstitium are the structures of the mammalian central nervous system (CNS) mainly affected by vitamin B(12) (cobalamin, Cbl) deficiency. Most of the response to the damage caused by Cbl deficiency seems to come from astrocytes and microglia, and is manifested as an increase in the number of cells positive for glial fibrillary acidic protein, the presence of ultrastructural signs of activation, and changes in cytokine and growth factor production and secretion. Myelin damage particularly affects the lamellae, which are disorganized by edema, as is the interstitium. Surprisingly, rat Schwann cells (myelin-forming cells of the peripheral nervous system) are fully activated but the few oligodendrocytes (myelin-forming cells of the CNS) are scarcely activated. The presence of intramyelin and interstitial edema raises questions about the integrity of the blood-brain barrier and blood-cerebrospinal fluid (CSF) barrier. The results obtained in the CNS of Cbl-deficient rats indicate that cytokine and growth factor imbalance is a key point in the pathogenesis of Cbl-deficient neuropathy. In the rat, Cbl deficiency increases the spinal cord (SC) synthesis and CSF levels of myelinotoxic cytokines (tumor necrosis factor (TNF)-alpha and soluble (s) CD40:sCD40 ligand dyad) and a myelinotoxic growth factor (nerve growth factor), but decreases SC synthesis and CSF levels of a myelinotrophic cytokine (interleukin-6) and a myelinotrophic growth factor (epidermal growth factor, EGF). The in vivo administration of IL-6 or EGF, or agents antagonizing the excess myelinotoxic agent, is as effective as Cbl in repairing or preventing Cbl-deficiency-induced CNS lesions. An imbalance in TNF-alpha and EGF levels has also been found in the CSF and serum of patients with severe Cbl deficiency.

PMID: 19394404 [PubMed - as supplied by publisher]

Stroke. 2009 May;40(5):1623-6. Epub 2009 Mar 12.

Periventricular white matter lucencies relate to low vitamin B12 levels in patients with small vessel stroke.

Pieters B, **Staals J**, **Knottnerus I**, **Rouhl R**, **Menheere P**, **Kessels A**, **Lodder J**.

Department of Neurology, University Hospital Maastricht, Maastricht, the Netherlands.

BACKGROUND AND PURPOSE: Blood-brain barrier dysfunction may be an early phenomenon in the development of the small vessel disease, which underlies white matter lesions. Because vitamin B12 plays a role in maintaining the integrity of the blood-brain barrier, we studied serum vitamin B12 level in relation to such lesions. METHODS: In 124 patients with first lacunar stroke, we measured serum vitamin B12 level and rated the degree of white matter lesions on MRI. RESULTS: Mean vitamin B12 level was 202 pmol/L (SD, 68.9). Thirty-nine patients (31.5%) had a vitamin B12 level less than the lower reference value of 150 pmol/L. Lower vitamin B12 level was (statistically significant) associated with more severe periventricular white matter lesions (odds ratio/100 pmol/L decrease, 1.773; 95% CI, 1.001-3.003), but not with deep white matter lesions (odds ratio/100 pmol/L decrease, 1.441; 95% CI, 0.881-2.358; ordered multivariate regression analysis). CONCLUSIONS: More severe periventricular white matter lesions in lacunar stroke patients relate to lower vitamin B12 levels. A possible causal relationship should now be studied prospectively.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 19286604 [PubMed - indexed for MEDLINE]

Rev Neurol. 2009 Apr 16-30;48(8):444-5.

[Nutritional deficiency of vitamin B12 in infancy as a cause of encephalopathy]

[Article in Spanish]

Mahfoud A, **Domínguez CL**, **Rodríguez D**, **Giamporcaro R**.

Publication Types:

- Case Reports
- Letter

PMID: 19340788 [PubMed - indexed for MEDLINE]

Food Nutr Bull. 2008 Dec;29(4):249-54.

Vitamin B12 status of pregnant Indian women and cognitive function in their 9-year-old children.

Bhate V, **Deshpande S**, **Bhat D**, **Joshi N**, **Ladkat R**, **Watve S**, **Fall C**, **de Jager CA**, **Refsum H**, **Yajnik C**.

Kamalnayan Bajaj Diabetology Research Center, Pune, India.

BACKGROUND: Recent research has highlighted the influence of maternal factors on the health of the offspring. Intrauterine experiences may program metabolic, cardiovascular, and psychiatric disorders. We have shown that maternal vitamin B12 status affects adiposity and insulin resistance in the child. Vitamin B12 is important for brain development and function. OBJECTIVE: We investigated the relationship between maternal plasma vitamin B12 status during pregnancy and the child's cognitive function at 9 years of age. METHODS: We studied children born in the Pune Maternal Nutrition Study. Two groups of children were selected on the basis of maternal plasma vitamin B12 concentration at 28 weeks of gestation: group 1 (n = 49) included children of mothers with low plasma vitamin B12 (lowest decile, < 77 pM) and group 2 (n = 59) children of mothers with high plasma vitamin B12 (highest decile, > 224 pM). RESULTS: Children from group 1 performed more slowly than those from group 2 on the Color Trail A test (sustained attention, 182 vs. 159 seconds; $p < .05$) and the Digit Span Backward test (short-term memory, $p < .05$), after appropriate adjustment for confounders. There were no differences between group 1 and group 2 on other tests of cognitive function (intelligence, visual agnosia). CONCLUSIONS: Maternal vitamin B12 status in pregnancy influences cognitive function in offspring.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 19227049 [PubMed - indexed for MEDLINE]

PMCID: PMC2656635

Nutr Neurosci. 2009 Feb;12(1):13-20.

Maternal MTHFR 677C>T genotype and dietary intake of folate and vitamin B(12): their impact on child neurodevelopment.

del Río Garcia C, **Torres-Sánchez L**, **Chen J**, **Schnaas L**, **Hernández C**, **Osorio E**, **Portillo MG**, **López-Carrillo L**.

Instituto Nacional de Salud Pública, Morelos, Mexico.

Using the Bayley test, the mental and psychomotor development in a cohort of 253 children were evaluated. Maternal dietary intake of vitamin B(12) and folate was assessed from a semiquantitative questionnaire administered during the first trimester of pregnancy. Maternal genotypes of MTHFR (677C>T and 1298A>C), were ascertained by PCR-RFLP. The 677T and 1298C variant alleles were present in 59% and 10% of participants, respectively. A dietary deficiency of vitamin B(12) was negatively associated with mental development (beta = -1.6; 95% CI = -2.8 to -0.3). In contrast, dietary intake of folate (< 400 mg/day) reduced the mental development index only among children of mothers who were carriers of the TT genotype (beta = -1.8; 95% CI = -3.6 to -0.04; P for interaction = 0.07). Vitamin B(12) and folate supplementation during pregnancy could have a favorable impact on the mental development of children during their first year of life, mainly in populations that are genetically susceptible.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't

PMID: 19178787 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2009 Feb;89(2):707S-11S. Epub 2008 Dec 30.

Vitamin B-12 and cognition in the elderly.

Smith AD, **Refsum H**.

Oxford Project to Investigate Memory and Ageing, the Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, United Kingdom. david.smith@pharm.ox.ac.uk

Vitamin B-12 deficiency is often associated with cognitive deficits. Here we review evidence that cognition in the elderly may also be adversely affected at concentrations of vitamin B-12 above the traditional cutoffs for deficiency. By using markers such as holotranscobalamin and methylmalonic acid, it has been found that cognition is associated with vitamin B-12 status across the normal range. Possible mediators of this relation include brain atrophy and white matter damage, both of which are associated with low vitamin B-12 status. Intervention trials have not been adequately designed to test whether these associations are causal. Pending the outcome of better trials, it is suggested that the elderly in particular should be encouraged to maintain a good, rather than just an adequate, vitamin B-12 status by dietary means.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 19116332 [PubMed - indexed for MEDLINE]

J Neurol Neurosurg Psychiatry. 2009 Feb;80(2):149-57. Epub 2008 Oct 31.

Plasma vitamin B12 status and cerebral white-matter lesions.

de Lau LM, **Smith AD**, **Refsum H**, **Johnston C**, **Breteler MM**.

Department of Epidemiology and Biostatistics, Erasmus Medical Centre, Rotterdam, The Netherlands.

BACKGROUND AND OBJECTIVE: Elevated homocysteine has been associated with a higher prevalence of cerebral white-matter lesions and infarcts, and worse cognitive performance. This raises the question whether factors involved in homocysteine metabolism, such as vitamin B(12), are also related to these outcomes. This study examined the association of several markers of vitamin B(12) status with cerebral white-matter lesions, infarcts and cognition. METHODS: The study evaluated the association of plasma concentrations of vitamin B(12), methylmalonic acid, holotranscobalamin and transcobalamin saturation with cerebral white-matter lesions and infarcts at baseline and cognition at baseline and during follow-up among 1019 non-demented elderly participants of the population-based Rotterdam Scan Study. Analyses were adjusted for several potential confounders, including homocysteine and folate concentration. RESULTS: Poorer vitamin B(12) status was significantly associated with greater severity of white-matter lesions, in particular periventricular white-matter lesions, in a concentration-related manner. Adjustment for common vascular risk factors (including blood pressure, smoking, diabetes and intima media thickness) did not alter the associations. Adjustment for homocysteine and folate modestly weakened the associations. No association was observed for any of the studied markers of vitamin B(12) status with presence of brain infarcts and baseline cognition or cognitive decline during follow-up. CONCLUSIONS: These results indicate that vitamin B(12) status in the normal range is associated with severity of white-matter lesions, especially periventricular lesions. Given the absence of an association with cerebral infarcts, it is hypothesised that this association is explained by effects on myelin integrity in the brain rather than through vascular mechanisms.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18977824 [PubMed - indexed for MEDLINE]

Neurology. 2008 Sep 9;71(11):826-32.

Vitamin B12 status and rate of brain volume loss in community-dwelling elderly.

Vogiatzoglou A, Refsum H, Johnston C, Smith SM, Bradley KM, de Jager C, Budge MM, Smith AD.

Department of Physiology, Anatomy and Genetics, University of Oxford, Le Gros Clark Building, South Parks Rd., Oxford OX1 3QX, UK.
anna.vogiatzoglou@dpag.ox.ac.uk

OBJECTIVES: To investigate the relationship between markers of vitamin B(12) status and brain volume loss per year over a 5-year period in an elderly population. METHODS: A prospective study of 107 community-dwelling volunteers aged 61 to 87 years without cognitive impairment at enrollment. Volunteers were assessed yearly by clinical examination, MRI scans, and cognitive tests. Blood was collected at baseline for measurement of plasma vitamin B(12), transcobalamin (TC), holotranscobalamin (holoTC), methylmalonic acid (MMA), total homocysteine (tHcy), and serum folate. RESULTS: The decrease in brain volume was greater among those with lower vitamin B(12) and holoTC levels and higher plasma tHcy and MMA levels at baseline. Linear regression analysis showed that associations with vitamin B(12) and holoTC remained significant after adjustment for age, sex, creatinine, education, initial brain volume, cognitive test scores, systolic blood pressure, ApoE epsilon4 status, tHcy, and folate. Using the upper (for the vitamins) or lower tertile (for the metabolites) as reference in logistic regression analysis and adjusting for the above covariates, vitamin B(12) in the bottom tertile (<308 pmol/L) was associated with increased rate of brain volume loss (odds ratio 6.17, 95% CI 1.25-30.47). The association was similar for low levels of holoTC (<54 pmol/L) (odds ratio 5.99, 95% CI 1.21-29.81) and for low TC saturation. High levels of MMA or tHcy or low levels of folate were not associated with brain volume loss. CONCLUSION: Low vitamin B(12) status should be further investigated as a modifiable cause of brain atrophy and of likely subsequent cognitive impairment in the elderly.

PMID: 18779510 [PubMed - indexed for MEDLINE]

Food Nutr Bull. 2008 Jun;29(2 Suppl):S126-31.

Effects of vitamin B12 and folate deficiency on brain development in children.

Black MM.

Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. mblack@peds.umaryland.edu

Folate deficiency in the periconceptional period contributes to neural tube defects; deficits in vitamin B12 (cobalamin) have negative consequences on the developing brain during infancy; and deficits of both vitamins are associated with a greater risk of depression during adulthood. This review examines two mechanisms linking folate and vitamin B12 deficiency to abnormal behavior and development in infants: disruptions to myelination and inflammatory processes. Future investigations should focus on the relationship between the timing of deficient and marginal vitamin B12 status and outcomes such as infant growth, cognition, social development, and depressive symptoms, along with prevention of folate and vitamin B12 deficiency.

Publication Types:

- Review

PMID: 18709887 [PubMed - indexed for MEDLINE]

Brain Res. 2008 Jan 10;1188:122-31. Epub 2007 Nov 1.

Effects of a B-vitamin-deficient diet on exploratory activity, motor coordination, and spatial learning in young adult Balb/c mice.

Lalonde R, **Barraud H**, **Ravey J**, **Guéant JL**, **Bronowicki JP**, **Strazielle C**.

Centre Hospitalier de l'Université de Montréal/St-Luc, Unité de Recherche en Sciences Neurologiques, Montréal, Canada. robert.lalonde@umontreal.ca

Elevated homocysteine levels resulting from vitamin B deficiencies have been hypothesized to contribute to functional decline. To investigate the effects of elevated serum homocysteine on neurobehavioral performances, young adult Balb/c mice consumed a vitamin-B-deficient diet or a control diet under free-feeding and pair-fed conditions. The B-deficient diet decreased body weight and food intake but increased water ingestion. Relative to either control group, vitamin-B-deficient mice were more active in the open field and in enclosed arms of the elevated plus-maze. However, vitamin-B-deficient mice were not impaired on sensorimotor coordination and spatial learning tests, swimming to a visible platform even faster than either control group. The main effect of this diet restriction was hyperactivity with no change in anxiety, coordination, and memory. It remains to be determined whether severer deficits are demonstrable in older mice.

PMID: 18061153 [PubMed - indexed for MEDLINE]

Clin Chem Lab Med. 2007;45(12):1614-20.

Biomarkers of folate and vitamin B(12) status in cerebrospinal fluid.

Herrmann W, **Obeid R**.

Department of Clinical Chemistry and Laboratory Medicine, Faculty of Medicine, University Hospital of Saarland, Homburg/Saar, Germany.
kchwher@uniklinikum-saarland.de

Folate and vitamin B(12) are essential cofactors for the methionine/homocysteine cycle in the brain. These vitamins mediate the remethylation of homocysteine (Hcy), which affects the production of the universal methyl donor, S-adenosylmethionine (SAM), in the brain among other organs. Additionally, increased plasma concentrations of total Hcy (tHcy) are associated with cerebrovascular disease and can compromise the blood-brain barrier. tHcy concentrations in the brain and cerebrospinal fluid become increased in several psychiatric and neurological disorders. Disturbances in the transmethylation pathway indicated by abnormal SAM, S-adenosylhomocysteine or their ratio have been reported in many neurodegenerative diseases, such as dementia, depression or Parkinson's disease. Cobalamin is essential for neuronal generation and its deficiency can cause degeneration of the nervous system. Available data emphasize that deficiency of folate and vitamin B(12) can lead to elevated concentrations of tHcy and disturbed methylation potential in the brain. Therefore, acquired or inherited disorders in these metabolic pathways are associated with brain abnormalities and severe neurological symptoms that are mostly irreversible, even after providing the missing cofactors. This review discusses the relationship between brain and blood levels of key vitamins and metabolites related to one carbon metabolism.

Publication Types:

- Review

PMID: 17892439 [PubMed - indexed for MEDLINE]

Z Geburtshilfe Neonatol. 2007 Aug;211(4):157-61.

[Maternal vitamin B12 deficiency: cause for neurological symptoms in infancy]

[Article in German]

Lücke T, **Korenke GC**, **Poggenburg I**, **Bentele KH**, **Das AM**, **Hartmann H**.

Klinik für Kinder und Jugendliche, Medizinische Hochschule Hannover.

BACKGROUND: Symptoms of Vitamin B (12) deficiency in infancy include growth retardation, regression of psychomotor development, muscular hypotonia and brain atrophy. Besides an inappropriate vegetarian diet of the infants, a vegan diet or a pernicious anaemia of the mother may lead to an insufficient vitamin B (12) supply of the child. PATIENTS AND METHODS: We report here the neurological symptoms of 4 fully breast-fed infants from mothers on vegan diet or with pernicious anaemia. DISCUSSION AND CONCLUSION: Vitamin B (12) deficiency can easily be diagnosed by detection of methylmalonic acid when measuring the organic acids in urine. Vitamin B (12) deficiency should be avoided or diagnosed as early as possible since a supplementation of mother and child can prevent neurological symptoms of the baby. Furthermore, the neurological symptoms of the infant with manifest vitamin B (12) deficiency are (partially) reversible.

Publication Types:

- Case Reports
- English Abstract

PMID: 17729202 [PubMed - indexed for MEDLINE]

Zhonghua Yu Fang Yi Xue Za Zhi. 2007 May;41(3):212-4.

[Effects of folic acid, vitamin B(6) and vitamin B(12) on learning and memory function in cerebral ischemia rats]

[Article in Chinese]

Huang GW, **Liu H**, **Wang YM**, **Ren DL**.

Nutrition Research Unit, School of Public Health, Tianjin Medical University, Tianjin 300070, China. guoweihuang@yahoo.com.cn

OBJECTIVE: To investigate the effects of folic acid, vitamin B(6) and B(12) on plasma homocysteine and on learning and memory functions in focal cerebral ischemia rats. METHODS: Sprague-Dawley rats were randomly divided into four groups. They were sham operation group (Sham OP), middle cerebral artery occlusion model group (MCAO), MCAO + folic acid group (MCAO + FA) and MCAO + compound vitamin (folate, vitamin B(6) and B(12)) group (MCAO + CV). Plasma homocysteine was measured before and after supplementation and after ischemia. RESULTS: The level of plasma homocysteine in MCAO + FA and MCAO + CV groups were significantly lower than those in Sham OP and MCAO groups after supplementation and ischemia (6.92 +/- 1.04) micromol/L and (5.49 +/- 1.00) micromol/L vs (9.33 +/- 1.11) micromol/L, (10.90 +/- 2.03 micromol/L), $P < 0.05$. While in MCAO + CV group was lower than that in MCAO + FA group (5.49 +/- 1.00) micromol/L vs (6.92 +/- 1.04) micromol/L, $P < 0.05$. The neurological deficit scores and shock times in Y-type maze of MCAO + FA and MCAO + CV groups were lower than those in MCAO group (1.75 +/- 0.46 and 1.38 +/- 0.52 vs 2.62 +/- 0.52; 123.50 +/- 39.77 and 86.25 +/- 21.39 vs 173.25 +/- 46.32, $P < 0.05$). The correct times of MCAO + CV group in Y-type maze was higher than that in MCAO group (3.75 +/- 0.42 vs 2.12 +/- 0.45, $P < 0.05$). CONCLUSION: Folic acid intake could not only reduce plasma homocysteine concentration but also promote the recovery of the learning and memory functions of rats with cerebral ischemia. The effects of folic acid combined with vitamin B(6) and vitamin B(12) on cerebral ischemia rats was better than that of single folate.

PMID: 17708876 [PubMed - indexed for MEDLINE]

Ann Univ Mariae Curie Sklodowska Med. 2004;59(2):408-9.

Vitamin B12 deficiency as a potential cause of dementia.

Pilarczyk M, **Porebiak J**, **Fidor A**, **Nastaj M**, **Jaworski J**, **Stelmasiak Z**.

Chair and Department of Neurology, Skubiszewski Medical University of Lublin.

There is a patient case with dementia and brain MRI massive abnormalities, probably in the course of vitamin B12 deficiency.

Publication Types:

- Case Reports

PMID: 16146118 [PubMed - indexed for MEDLINE]

Rev Neurol. 2005 May 16-31;40(10):605-8.

[Encephalopathy with methylmalonic aciduria and homocystinuria secondary to a deficient exogenous supply of vitamin B12]

[Article in Spanish]

Gutiérrez-Aguilar G, **Abenia-Usón P**, **García-Cazorla A**, **Vilaseca MA**, **Campistol J**.

Servicio de Neurología, Unitat Integrada Hospital Sant Joan de Deu-Clinic, E-08950 Esplugues de Llobregat, Spain.

INTRODUCTION: A deficient supply of vitamin B12 can appear early during the first months of life, with haematological and neurological symptoms in the form of progressive encephalopathy. CASE REPORTS: We describe two patients with megaloblastic anaemia and halted somatic and cranial perimeter development, accompanied by neurological involvement. Both of them had an increased rate of excretion of methylmalonic acid, as well as homocysteine, in urine with extremely low serum levels of vitamin B12, as compared to normal values. Both patients were breastfed only. The study of the mothers revealed asymptomatic pernicious anaemia. Treatment with hydroxycobalamine led to clinical recovery and psychomotor development progressively returned to normal. CONCLUSIONS: Vitamin B12 deficiency due to a shortage of supply from the mother must be taken into account in the differential diagnosis of possibly reversible severe encephalopathies.

Publication Types:

- Case Reports
- English Abstract

PMID: 15926134 [PubMed - indexed for MEDLINE]

Acta Neurol Belg. 2004 Dec;104(4):173-5.

Masked deficit of vitamin B12 in the patient with heterozygous beta-thalassemia and spastic paraparesis.

Bilic E, **Bilic E**, **Zagar M**, **Juric S**.

Department of Pediatric Haematology, University Hospital Centre Zagreb, Croatia. ernest.bilic@zg.htnet.hr

The spinal cord, brain, optic nerves and peripheral nerves may be affected by vitamin B12 (cobalamin) deficiency. Deficiency of vitamin B12 also causes megaloblastic anaemia, meaning that the red blood cells are usually larger than normal. In this paper we report a 16-year old girl who was referred to us for the evaluation of mild paraparesis and paresthesias marked by tingling "pins and needles" feelings and general weakness. The patient, her parents and sisters were on a strict vegan diet, which made us believe that vitamin B12 deficiency may be the possible cause of the neurologic clinical manifestations. The serum level of vitamin B12 was low, but there was no macrocytosis in the routine blood examination. The electrophoresis of haemoglobin was pathologic, there was 3.7% of HbA2 and 11.6% of HbF (heterozygous form of beta-thalassaemia). When megaloblastic anaemia occurs in combination with a condition that gives rise to microcytic anaemia, many megaloblastic features may be masked. Instead of being macrocytic, the anaemia could be normocytic or even microcytic. Vitamin B12 deficiency is a diagnosis that must not be overlooked. This case report turns the light on the fact that increased MCV is a hallmark in vitamin B12 deficiency, but it is not an obligatory sign.

Publication Types:

- Case Reports
- Research Support, Non-U.S. Gov't

PMID: 15742609 [PubMed - indexed for MEDLINE]

Vitamin B-12 and Psychiatric Disorders

J Indian Med Assoc. 2007 Jul;105(7):395-6.

Psychiatric presentations of vitamin B 12 deficiency.

Bhat AS, **Srinivasan K**, **Kurpad SS**, **Galgali RB**.

Department of Psychiatry, St John's Medical College Hospital, Bangalore.

Vitamin B12 deficiency has been implicated in various psychiatric conditions for a long time. The association could be primary, secondary to the psychiatric disorder, or even just coincidental. However, left untreated, the deficiency can delay or preclude recovery. Hence early recognition is important, especially when the traditional manifestations of B12 deficiency like anaemia, macrocytosis or spinal cord symptoms are not prominent. Three cases are presented here where vitamin B12 deficiency and psychiatric symptomatology were coexistent, and the patients recovered only on a combination of B12 supplementation and psychiatric medication.

PMID: 18178994 [PubMed - indexed for MEDLINE]

J Assoc Physicians India. 2008 Feb;56:115-6.

Chronic psychosis associated with vitamin B12 deficiency.

Rajkumar AP, **Jebaraj P**.

Department of Psychiatry, Christian Medical College, Vellore-632002, Tamil Nadu, India.

B12 deficiency is widely prevalent and usually presents with haematologic and neuropsychiatric manifestations. Psychiatric symptoms seldom precede anaemia and present as the principal manifestation of B12 deficiency. A report an unusual presentation of long standing psychotic symptoms without anaemia in a 31 year old male, who presented to a tertiary care psychiatric facility. His physical examination revealed hyper pigmentation of extremities and posterior column involvement. Laboratory investigations confirmed normal haemoglobin and low serum B12 levels. He recovered dramatically with short term anti psychotic medication and intramuscular cobalamin supplementation. He remained asymptomatic and functionally independent at two years follow up.

Publication Types:

- Case Reports

PMID: 18472513 [PubMed - indexed for MEDLINE]

Psychiatr Clin North Am. 2007 Dec;30(4):739-59.

Hematologic problems in psychosomatic medicine.

Becker M, **Axelrod DJ**, **Oyesanmi O**, **Markov DD**, **Kunkel EJ**.

Department of Psychiatry, Thomas Jefferson University, Philadelphia, PA, USA.

Vitamin B12 deficiency is associated with problems in cognition, mood, psychosis, and less commonly, anxiety. Folate deficiency primarily is associated with problems in mood. Patients who have sickle cell disease, a disease of chronic pain, experience difficulties with depression, anxiety, stigma, and are at risk for substance abuse and dependence. Patients with hemophilia have benefited from advances in treatment; however, their morbidity and mortality were compounded in those who received blood products contaminated with HIV, or hepatitis B and C. Psychiatrists who practice psychosomatic medicine should expect to encounter patients with the above problems, as they are frequently seen in medical settings. Finally, most of the commonly used psychotropic medications have uncommon but potentially important hematologic side effects or may interact with the anticoagulants used in medically ill patients.

Publication Types:

- Review

PMID: 17938043 [PubMed - indexed for MEDLINE]

Prim Care Companion J Clin Psychiatry. 2007;9(3):238.

Vitamin b(12) deficiency manifested as mania: a case report.

Gomez-Bernal GJ, **Bernal-Perez M**.

Rehabilitation Unit, Psychiatric Hospital of Teruel, Teruel, Spain.

PMID: 17632664 [PubMed - in process]

PMCID: PMC1911186

Gen Hosp Psychiatry. 2008 Mar-Apr;30(2):185-6.

Role of vitamin B12 in depressive disorder--a case report.

Rao NP, **Kumar NC**, **Raman BR**, **Sivakumar PT**, **Pandey RS**.

Department of Psychiatry, National Institute of Mental Health and Neurosciences (Deemed University), Bangalore 560 029, India. docnaren@gmail.com

Vitamin B12 deficiency anemia may have psychiatric manifestations preceding the hematological symptoms. Although a variety of symptoms are described, there are only sparse data on the role of vitamin B12 in depression. We report a case of vitamin B12 deficiency presenting with recurrent episodes of depression.

Publication Types:

- Case Reports

PMID: 18291301 [PubMed - indexed for MEDLINE]

Pediatr Emerg Care. 2008 Aug;24(8):538-41.

Neurological consequences of vitamin B12 deficiency and its treatment.

Chalouhi C, **Faesch S**, **Anthoine-Milhomme MC**, **Fulla Y**, **Dulac O**, **Chéron G**.

Département des urgences pédiatriques, Hôpital Necker Enfants Malades, Paris, France. christel.chalouhi@nck.ap-hop-paris.fr

In developed countries, the vitamin B12 deficiency usually occurs in children exclusively breast-fed, whose mothers are vegetarians, causing low stores of vitamin B12. Symptoms of vitamin B12 deficiency appear during the second trimester of life and include failure to thrive, lethargy, hypotonia, and arrest or regression of developmental skills. A megaloblastic anemia can be present. One half of the infants exhibit abnormal movements before the start of treatment with intramuscular cobalamin, which disappear 1 or 2 days after. More rarely, movement disorders appear a few days after treatment, whereas neurological symptoms are improving. These abnormal movements can last for 2 to 6 weeks. If not treated, vitamin B12 deficiency can cause lasting neurodisability. Therefore, efforts should be directed to preventing deficiency in pregnant and breast-feeding women on vegan diets and their infants by giving them vitamin B12 supplements. When preventive supplementation has failed, one should recognize and treat quickly an infant presenting with failure to thrive and delayed development.

Publication Types:

- Case Reports

PMID: 18708898 [PubMed - indexed for MEDLINE]

Nutr Rev. 2008 May;66(5):250-5.

Effect of vitamin B12 deficiency on neurodevelopment in infants: current knowledge and possible mechanisms.

Dror DK, **Allen LH**.

Department of Nutrition at the University of California Davis, Davis, California, USA. dkdror@ucdavis.edu

Severe vitamin B(12) deficiency produces a cluster of neurological symptoms in infants, including irritability, failure to thrive, apathy, anorexia, and developmental regression, which respond remarkably rapidly to supplementation. The underlying mechanisms may involve delayed myelination or demyelination of nerves; alteration in the S-adenosylmethionine:S-adenosylhomocysteine ratio; imbalance of neurotrophic and neurotoxic cytokines; and/or accumulation of lactate in brain cells. This review summarizes the current knowledge concerning infantile vitamin B(12) deficiency, including a pooled analysis of case studies of infants born to mothers with untreated pernicious anemia or a strict vegetarian lifestyle and a discussion of the mechanisms that may underlie the manifestations of deficiency.

Publication Types:

- Review

PMID: 18454811 [PubMed - indexed for MEDLINE]

Med Secoli. 2007;19(1):9-18.

New pathogenesis of the cobalamin-deficient neuropathy.

Scalabrino G, **Veber D**, **Mutti E**.

Institute of General Pathology and Center of Excellence on Neurodegenerative Diseases, University of Milan, Milano, I.

Subacute combined degeneration (SCD) is considered the neurological counterpart of pernicious anaemia because it is the paradigmatic neurological manifestation of acquired vitamin B12 (cobalamin (Cbl)) deficiency in adulthood. Hitherto, the theories advanced to explain the pathogenesis of SCD have postulated a causal relationship between SCD lesions and the impairment of either or both of two Cbl-dependent reactions. We have identified a new experimental model, the totally gastrectomised (TGX) rat, to reproduce the key morphological features of the disease, and found new mechanisms responsible for the pathogenesis of SCD. We have demonstrated that the neuropathological lesions in TGX rats are not only due to mere vitamin withdrawal but also to the overproduction of the myelinolytic tumour necrosis factor (TNF)-alpha, nerve growth factor, the soluble(s) CD40:sCD40 ligand dyad, and the reduced synthesis of the neurotrophic agents, epidermal growth factor and interleukin-6. Cbl replacement treatments normalised all of these abnormalities.

Publication Types:

- Historical Article

PMID: 18447164 [PubMed - indexed for MEDLINE]

J Med Case Reports. 2008 Mar 21;2:90.

Neuropathy caused by B12 deficiency in a patient with ileal tuberculosis: A case report.

Toosi TD, **Shahi F**, **Afshari A**, **Roushan N**, **Kermanshahi M**.

Imam Khomeini Hospital, Tehran University of Medical Sciences, Keshavarz Blvd,, Tehran, Iran. dormohammadi@tums.ac.ir.

ABSTRACT: INTRODUCTION: Vitamin B12 deficiency can result in macrocytic anemia. Neurologic abnormalities of B12 deficiency include sensory deficits, loss of deep tendon reflexes, movement disorders, neuropsychiatric changes and seizures. Segmental involvement of the distal ileum, such as in tuberculosis, can cause vitamin B12 deficiency. To our knowledge, macrocytic anemia with unusual manifestations such as brain atrophy and seizures due to intestinal tuberculosis has not been reported in the literature. CASE PRESENTATION: A 14-year-old girl presented with complaints of paraplegia, ataxia, fever and fatigue that had started a few months earlier and which had been getting worse in the last three weeks. Her laboratory results were indicative of macrocytic anemia with a serum B12 level <100 (normal, 160-970) pg/ml and hypersegmented neutrophils. Her MRI findings showed brain atrophy. Her fever workup eventually led to the diagnosis of tuberculosis which was documented by bone marrow aspiration smear & culture. A small bowel series showed that tuberculosis had typically involved the terminal ileum which had resulted in vitamin B12 deficiency. She was treated for vitamin B12 deficiency and tuberculosis. Her fever ceased and her hemoglobin level returned to normal. At present, she can eat, write, and speak normally as well as walk and ride a bicycle. CONCLUSION: Vitamin B12 deficiency should be considered in patients with neurologic features such as paresthesia, sensory deficits, urinary incontinence, dysarthria, and ataxia. The underlying cause of B12 deficiency should be determined and treated to obviate the patients' need for long term vitamin B12 therapy.

PMID: 18355418 [PubMed - in process]

PMCID: PMC2329654

Dev Med Child Neurol. 2007 Oct;49(10):774-6.

West syndrome in an infant with vitamin B12 deficiency in the absence of macrocytic anaemia.

Erol I, **Alehan F**, **Gümüs A**.

Division of Child Neurology, Department of Paediatrics, Baskent University Faculty of Medicine, Ankara, Turkey. ilknur_erol@yahoo.com

Vitamin B(12) deficiency in infants often produces haematological and neurological deficits, including macrocytic anaemia, neurodevelopmental delay or regression, irritability, weakness, hypotonia, ataxia, apathy, tremor, and seizures. The diagnosis of vitamin B(12) deficiency can be difficult when the typical macrocytic anaemia is absent. We report the case of a 10-month-old female diagnosed with West syndrome associated with vitamin B(12) deficiency but without macrocytic anaemia caused by nutritional inadequacy in the mother. The patient's motor skills and cognitive development were normal until she was 9 months old, when she began to exhibit a series of sudden flexions of the head, trunk, arms, and legs. She was exclusively breast-fed and had received no vitamin supplementation. Results of electroencephalography (EEG) indicated modified hypsarrhythmia and the patient was diagnosed as having West syndrome. Synthetic adrenocorticotropic hormone was administered and although her spasms had resolved, the patient remained apathic and could not sit without assistance. EEG results indicated generalized slow activity. After she was diagnosed as having vitamin B(12) deficiency, parenteral treatment with vitamin B(12) was initiated. Her symptoms resolved and EEG was completely normal. When she was 20 months old she exhibited an age-appropriate developmental and neurological profile. To our knowledge, this is the first report of West syndrome as a presenting symptom of vitamin B(12) deficiency.

Publication Types:

- Case Reports

PMID: 17880648 [PubMed - indexed for MEDLINE]

Fortschr Neurol Psychiatr. 2007 Sep;75(9):515-27.

[Review of the role of hyperhomocysteinemia and B-vitamin deficiency in neurological and psychiatric disorders--current evidence and preliminary recommendations]

[Article in German]

Herrmann W, **Lorenzl S**, **Obeid R**.

Institut für Klinische Chemie und Laboratoriumsmedizin, Universitätsklinikum des Saarlandes, Kirrberger Strasse, Gebaude 57, 66421 Homburg. prof.wolfgang.herrmann@uni-klinikum-saarland.de

Elevated concentration of total homocysteine (Hcy) in plasma (> 12 micromol/l) is a risk factor for several diseases of the central nervous system. Epidemiological studies have shown a dose-dependent relationship between concentrations of Hcy and the risk for neurodegenerative diseases. Hcy is a marker for B-vitamin deficiency (folate, B12, B6). Hyperhomocysteinemia (HHcy) causes hypomethylation which is an important mechanism that links Hcy to dementia. Supplementation with vitamins B aims at reducing the risk of neurodegenerative diseases. Current evidence suggests that Hcy-lowering treatment has a positive effect for the secondary and primary prevention of stroke. HHcy is very common in patients with Parkinson disease particularly those who receive L-dopa treatment. Furthermore, a positive association has been reported between HHcy and multiple sclerosis. Moreover, HHcy and vitamin B deficiency are reported to have a causal role in depression, and epilepsy. In addition several anti-epileptic drugs cause secondary HHcy. Therefore, sufficient intakes of the vitamins are recommended for patients who have already developed neuropsychiatric diseases. Vitamin B deficiency should be suspected in children with development disorders, failure to thrive and unexplained neurological manifestations. Elderly people are also an important at-risk group where vitamin B deficiency and HHcy have been linked to neurodegenerative diseases. Treatment with folate, B12, and B6 can improve cerebral function. Preventive vitamin B supplementation and sufficient intake seem very important for secondary and primary prevention of neuropsychiatric disorders, especially in subjects with a low intake or status of the vitamins.

PMID: 17729191 [PubMed - indexed for MEDLINE]

Clin Chem. 2007 Feb;53(2):326-33. Epub 2007 Jan 2.

Biomarkers of folate and vitamin B12 are related in blood and cerebrospinal fluid.

Obeid R, **Kostopoulos P**, **Knapp JP**, **Kasoha M**, **Becker G**, **Fassbender K**, **Herrmann W**.

Department of Clinical Chemistry and Laboratory Medicine, Faculty of Medicine, University Hospital of Saarland, Homburg/Saar, Germany.

BACKGROUND: B-vitamins (folate, B(12)) are important micronutrients for brain function and essential cofactors for homocysteine (HCY) metabolism. Increased HCY has been related to neurological and psychiatric disorders. We studied the role of the B-vitamins in HCY metabolism in the brain. METHODS: We studied blood and cerebrospinal fluid (CSF) samples from 72 patients who underwent lumbar puncture. We measured HCY, methylmalonic acid (MMA), and cystathionine by gas chromatography-mass spectrometry; S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) by liquid chromatography-tandem mass spectrometry; and the B-vitamins by HPLC or immunoassays. RESULTS: Concentrations were lower in CSF than serum or plasma for HCY (0.09 vs 9.4 micromol/L), SAH (13.2 vs 16.8 nmol/L), cystathionine (54 vs 329 nmol/L), and holotranscobalamin (16 vs 63 pmol/L), whereas concentrations in CSF were higher for MMA (359 vs 186 nmol/L) and SAM (270 vs 113 nmol/L; all $P < 0.05$). CSF concentrations of HCY correlated significantly with CSF folate ($r = -0.46$), CSF SAH ($r = 0.48$), CSF-albumin ($r = 0.31$), and age ($r = 0.32$). Aging was also associated with lower concentrations of CSF-folate and higher CSF-SAH. The relationship between serum and CSF folate depended on serum folate: the correlation (r) of serum and CSF-folate was 0.69 at serum folate <15.7 nmol/L. CSF concentrations of MMA and holotranscobalamin were not significantly correlated. CONCLUSIONS: CSF and serum/plasma concentrations of vitamin biomarkers are significantly correlated. Older age is associated with higher CSF-HCY and CSF-SAH and lower CSF-folate. These metabolic alterations may be important indicators of low folate status, hyperhomocysteinemia, and neurodegenerative diseases.

PMID: 17200133 [PubMed - indexed for MEDLINE]

Vitamin B-12 and Anemia

Drug Ther Bull. 2009 Feb;47(2):19-21.

Oral or intramuscular vitamin B12?

[No authors listed]

Vitamin B(12) deficiency is common, becoming more so with age, and estimates of its population prevalence have ranged from 1.5% to 15%. If untreated, it can lead to megaloblastic anaemia and irreversible neurological complications. In the UK, the usual treatment is regular intramuscular injections of hydroxocobalamin. High-dose oral vitamin B(12) replacement is standard practice in some other countries and less costly. Here we review issues around adopting an oral vitamin B(12) replacement regimen more widely in the UK.

PMID: 19193702 [PubMed - in process]

J Am Acad Dermatol. 2009 Mar;60(3):498-500.

Glossitis with linear lesions: an early sign of vitamin B12 deficiency.

Graells J, **Ojeda RM**, **Muniesa C**, **Gonzalez J**, **Saavedra J**.

Department of Dermatology, Hospital de Sant Joan de Déu de Sant Boi de Llobregat, Barcelona, Spain. 26449jge@comb.es

The classic oral manifestations of vitamin B(12) deficiency are considered nonspecific. We describe 4 patients with oral linear lesions associated with vitamin B(12) deficiency. Patients were free of neurologic symptoms and anemia at diagnosis. We believe that glossitis with linear lesions is an early clinical sign of vitamin B(12) deficiency. We recommend the determination of vitamin B(12) in such patients, even in the absence of anemia.

Publication Types:

- Case Reports

PMID: 19231648 [PubMed - indexed for MEDLINE]

Am J Clin Nutr. 2009 Feb;89(2):702S-6S. Epub 2009 Jan 13.

Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency.

Selhub J, **Morris MS**, **Jacques PF**, **Rosenberg IH**.

Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111, USA. jacob.selhub@tufts.edu

Previous reports on pernicious anemia treatment suggested that high folic acid intake adversely influences the natural history of vitamin B-12 deficiency, which affects many elderly individuals. However, experimental investigation of this hypothesis is unethical, and the few existing observational data are inconclusive. With the use of data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES), we evaluated the interaction between high serum folate and low vitamin B-12 status [ie, plasma vitamin B-12 < 148 pmol/L or methylmalonic acid (MMA) > 210 nmol/L] with respect to anemia and cognitive impairment. With subjects having both plasma folate < or = 59 nmol/L and normal vitamin B-12 status as the referent category, odds ratios for the prevalence of anemia compared with normal hemoglobin concentration and impaired compared with unimpaired cognitive function were 2.1 (95% CI: 1.1, 3.7) and 1.7 (95% CI: 1.01, 2.9), respectively, for those with low vitamin B-12 status but normal serum folate and 4.9 (95% CI: 2.3, 10.6) and 5.0 (95% CI: 2.7, 9.5), respectively, for those with low vitamin B-12 status and plasma folate >59 nmol/L. Among subjects with low vitamin B-12 status, mean circulating vitamin B-12 was 228 pmol/L for the normal-folate subgroup and 354 pmol/L for the high-folate subgroup. We subsequently showed increases in circulating homocysteine and MMA concentrations with increasing serum folate among NHANES participants with serum vitamin B-12 < 148 pmol/L, whereas the opposite trends occurred among subjects with serum vitamin B-12 > or = 148 pmol/L. These interactions, which were not seen in NHANES III before fortification, imply that, in vitamin B-12 deficiency, high folate status is associated with impaired activity of the 2 vitamin B-12-dependent enzymes, methionine synthase and MMA-coenzyme A mutase.

PMID: 19141696 [PubMed - indexed for MEDLINE]

PMCID: PMC2647758 [Available on 2010/02/01]

Int J Lab Hematol. 2009 Feb;31(1):1-8. Epub 2008 Nov 19.

Oral cobalamin (vitamin B(12)) treatment. An update.

Andrès E, **Dali-Youcef N**, **Vogel T**, **Serraj K**, **Zimmer J**.

Department of Internal Medicine, Diabetes and Metabolic Diseases, Hôpitaux Universitaires de Strasbourg, Strasbourg, France. andres@chru-strasbourg.fr

The objective of this review was to evaluate oral cobalamin (vitamin B(12)) therapy in adult and elderly patients, from the perspective of a hematologist. PubMed was systematically searched for English and French articles published from January 1990 to January 2007. Data from our working group, the 'Groupe d'étude des carences en vitamine B(12)des Hôpitaux Universitaires de Strasbourg', have also been included. Several prospective studies in well-determined population (n = 4), prospective randomized studies (n = 3) and a systematic review by the Cochrane group (n = 1) provide evidence that oral cobalamin therapy may adequately treat cobalamin deficiency, particularly hematological abnormalities or manifestations. These studies suggest that at least 1000 microg/day of oral cyanocobalmin are needed for pernicious anemia and a mean daily dose of 250 microg for food-cobalamin malabsorption. This present review confirms the previously reported efficacy of oral cobalamin treatment in adult and elderly patients.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 19032377 [PubMed - indexed for MEDLINE]

Eur J Intern Med. 2008 Nov;19(7):488-93. Epub 2008 Mar 14.

Update of nutrient-deficiency anemia in elderly patients.

Andrès E, **Federici L**, **Serraj K**, **Kaltenbach G**.

Department of Internal Medicine, University Hospital of Strasbourg, Strasbourg, France. emmanuel.andres@chru-strasbourg.fr

Anemia, defined as a hemoglobin level < 13 g/dL in men and < 12 g/dL in women, is an important healthcare concern among the elderly. Nutrient-deficiency anemia represents one third of all anemias in elderly patients. About two thirds of nutrient-deficiency anemia is associated with iron deficiency and most of those cases are the result of chronic blood loss from gastrointestinal lesions. The remaining cases of nutrient-deficiency anemia are usually associated with vitamin B12, most frequently related to food-cobalamin malabsorption, and/or folate deficiency and are easily treated (nutrient-deficiency replacement).

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 19013375 [PubMed - indexed for MEDLINE]

South Med J. 2008 Oct;101(10):1024-31.

Anemia following Roux-en-Y surgery for morbid obesity: a review.

Marinella MA.

Department of Medicine, Division of Hematology-Oncology, Wright State University School of Medicine, Dayton, OH 45429, USA. MMarinella@pol.net

Morbid obesity is a significant problem in the Western world. Recently, there has been an increase in the number of patients undergoing surgical weight loss procedures. Currently, the most widely performed procedure is the Roux-en-Y gastric bypass operation which combines restriction of food intake with malabsorption of calories and various nutrients, resulting in weight loss and nutritional deficiencies, respectively. Various types of anemia may complicate Roux-en-Y and commonly include deficiencies of iron, folate, and vitamin B12. Iron deficiency is particularly common and may result from many mechanisms including poor intake, malabsorption, and mucosal bleeding from marginal ulceration. However, less appreciated etiologies of nutritional anemia include deficiencies of B-complex vitamins, ascorbic acid, and copper. Replacement of the missing or decreased constituent usually reverses the anemia. Since physicians of various medical and surgical specialties are often involved with the postoperative care of bariatric patients, a review of anemia in this patient population is warranted.

Publication Types:

- Review

PMID: 18791538 [PubMed - indexed for MEDLINE]

Klin Lab Diagn. 2008 Jul;(7):29-32.

[Morphometric characteristics of erythrocytes in B12-deficiency anemia (based on computer morphometric data)]

[Article in Russian]

Potapova SG, **Shishina RN**.

The paper presents the results of computed morphometry of peripheral red blood cells in elderly patients with B12-deficiency anemia before treatment. The study was performed in the fine Romanovsky-stained peripheral blood smears, by using an ASPEK Russian hematological cell image analyzer. The objective quantitative characteristics of the parameters of the major megaloblastic hematopoiesis markers (macro- and megalocytes) in peripheral blood are given. The composition of peripheral blood was determined from the content of red blood cells with varying amounts of hemoglobin.

Publication Types:

- English Abstract

PMID: 18756730 [PubMed - indexed for MEDLINE]

Food Nutr Bull. 2008 Jun;29(2 Suppl):S188-95.

Review of interventions for the prevention and control of folate and vitamin B12 deficiencies.

Cordero JF, **Do A**, **Berry RJ**.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA. jcordero@rcm.upr.edu

Folate and vitamin B12 deficiencies represent important and evolving global health challenges that contribute to the global burden of anemia, neurologic conditions, neurodevelopmental disorders, and birth defects. We present a review of population-based programs designed to increase consumption of folates and vitamin B12. A folic acid supplementation program targeting couples prior to marriage in China has led to optimal consumption of supplements containing folic acid and a significant reduction of neural tube defects (NTD). Supplementation programs that use mass community education show some promise, but have not been shown to be as effective as targeted education. The success of supplementation programs hinges on a strong and persistent educational component and access to the supplements. Fortification with folic acid has been shown to reduce the prevalence of NTD in the countries where it has been implemented. Challenges to fortification programs include identifying the appropriate delivery vehicles, setting the optimal fortification level, sustaining the quality assurance of the fortification level, and addressing regulatory challenges and trade barriers of commercially fortified flours. Supplementation and fortification are cost-effective and viable approaches to reducing the burden of NTD, anemia, and other conditions resulting from folate deficiency. The experience with interventions involving folic acid could provide a model for the subsequent development of supplementation and fortification programs involving vitamin B12.

Publication Types:

- Review

PMID: 18709892 [PubMed - indexed for MEDLINE]

Ann Hematol. 2008 Dec;87(12):949-59. Epub 2008 Jul 19.

Prepartum anaemia: prevention and treatment.

Milman N.
Department of Obstetrics and Gynaecology, Gentofte Hospital, University of Copenhagen, Hellerup, Copenhagen, Denmark. nils.mil@dadlnet.dk

This review focuses on the occurrence, prevention and treatment of anaemia during pregnancy in Western societies. Iron deficiency anaemia (IDA) is the most prevalent deficiency disorder and the most frequent form of anaemia in pregnant women. Minor causes of anaemia are folate and vitamin B12 deficiency, haemoglobinopathy and haemolytic anaemia. Anaemia is defined as haemoglobin of <110 g/L in the first and third trimester and <105 g/L in the second trimester. The diagnosis relies on haemoglobin, a full blood count and plasma ferritin, which can be supported by plasma transferrin saturation and serum soluble transferrin receptor. Among fertile, non-pregnant women, approximately 40% have ferritin of <or=30 microg/L, i.e. small or absent iron reserves and therefore an unfavourable iron status with respect to upcoming pregnancy. The prevalence of prepartum anaemia in the third trimester ranges 14-52% in women taking placebo and 0-25% in women taking iron supplements, dependent on the doses of iron. In studies incorporating serum ferritin, the frequency of IDA in placebo-treated women ranges 12-17% and in iron-supplemented women 0-3%. Requirements for absorbed iron increase during pregnancy from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester, on the average approximately 4.4 mg/day, and dietary measures are inadequate to reduce the frequency of prepartum IDA. However, IDA is efficiently prevented by oral iron supplements in doses of 30-40 mg ferrous iron taken between meals from early pregnancy to delivery. Treatment of IDA should aim at replenishing body iron deficits by oral and/or intravenous administration of iron. In women with slight to moderate IDA, i.e. haemoglobin of 90-105 g/L, treatment with oral ferrous iron of approximately 100 mg/day between meals is the therapeutic option in the first and second trimester; haemoglobin should be checked after 2 weeks and provided an increase of >or=10 g/L, oral iron therapy has proved effective and should continue. Treatment with intravenous iron is superior to oral iron with respect to the haematological response. Intravenous iron is considered safe in the second and third trimester, while there is little experience in the first trimester. Intravenous iron of 600-1,200 mg should be considered: (1) as second option if oral iron fails to increase haemoglobin within 2 weeks; (2) as first option at profound IDA, i.e. haemoglobin of <90 g/L in any trimester beyond 14 weeks gestation; and (3) as first option for IDA in third trimester. Profound IDA has serious consequences for both woman and foetus and requires prompt intervention with intravenous iron. This is especially important for the safety of women who for various reasons oppose blood transfusions.

Neth J Med. 2008 May;66(5):216-7.

Anaemia and haemolysis in pregnancy due to rapid folic acid and vitamin B12 depletion.

van Gellekom SA, Lindauer-van der Werf G, Hague WM, de Vries JI.

Publication Types:

- Case Reports
- Letter

PMID: 18490802 [PubMed - indexed for MEDLINE]

J Pediatr. 2008 May;152(5):731-3.

Neonatal vitamin B12 deficiency secondary to maternal subclinical pernicious anemia: identification by expanded newborn screening.

Marble M, **Copeland S**, **Khanfar N**, **Rosenblatt DS**.

Department of Pediatrics, Division of Clinical Genetics, Louisiana State University Health Sciences Center, Children's Hospital of New Orleans, New Orleans, LA, USA. mmarbl1@lsuhsc.edu

A neonate with elevated propionylcarnitine on the newborn screen was found to have methylmalonic acidemia due to vitamin B(12) deficiency. The mother was also vitamin B(12)-deficient. This case illustrates the utility of expanded newborn screening for detection of vitamin B(12) deficiency, allowing prompt treatment and prevention of potential sequelae.

Publication Types:

- Case Reports

PMID: 18410783 [PubMed - indexed for MEDLINE]

Eur J Haematol. 2008 May;80(5):448-51. Epub 2008 Jan 23.

Severe vitamin B12 deficiency resulting in pancytopenia, splenomegaly and leukoerythroblastosis.

Halfdanarson TR, **Walker JA**, **Litzow MR**, **Hanson CA**.

Department of Internal Medicine, Division of Hematology, Mayo Clinic College of Medicine, Rochester, MN, USA. thorvardur-halfdanarson@uiowa.edu

Deficiency of vitamin B12 is a well known cause of megaloblastic anemia and pancytopenia. Splenomegaly and leukoerythroblastosis are much less well known manifestations of B12 deficiency. We report a B12 deficient female with severe pancytopenia including normocytic anemia who also had enlarged spleen and circulating nucleated red blood cells as well as circulating immature myeloid cells. Although these findings are reported in the earlier literature, more modern reviews of the subject often fail to mention this association. We review the literature on these unusual manifestations of B12 deficiency and remind clinicians that splenomegaly and erythroblastosis can serve as diagnostic clues in cases of severe megaloblastic anemia secondary to B12 deficiency.

Publication Types:

- Case Reports

PMID: 18221385 [PubMed - indexed for MEDLINE]

Eksp Klin Gastroenterol. 2005;(6):33-6, 112-3.

[Clinical and morphological characteristics of chronic gastritis complicated with B12- and iron-deficiency anemia]

[Article in Russian]

Vorob'ev SA.

There was a study of 49 patients with iron- and B12-deficiency anemia. Morphological symptoms of chronic gastritis were revealed in 100% of patients. Chronic gastritis against the background of iron-deficiency anemia was characterized by superficial and focal atrophic lesions of the antral mucous coat, frequently--by erosions, and clinical manifestations in the form of intestinal indigestion and abdominal pains. Chronic gastritis against the background of B12-deficiency anemia always had an atrophic nature, was localized in the body and in the antral part of the stomach, and had clinical manifestations in the form of intestinal indigestion.

Publication Types:

- English Abstract

PMID: 17378384 [PubMed - indexed for MEDLINE]

Eur J Haematol. 2008 May;80(5):448-51. Epub 2008 Jan 23.

Severe vitamin B12 deficiency resulting in pancytopenia, splenomegaly and leukoerythroblastosis.

Halfdanarson TR, **Walker JA**, **Litzow MR**, **Hanson CA**.

Department of Internal Medicine, Division of Hematology, Mayo Clinic College of Medicine, Rochester, MN, USA. thorvardur-halfdanarson@uiowa.edu

Deficiency of vitamin B12 is a well known cause of megaloblastic anemia and pancytopenia. Splenomegaly and leukoerythroblastosis are much less well known manifestations of B12 deficiency. We report a B12 deficient female with severe pancytopenia including normocytic anemia who also had enlarged spleen and circulating nucleated red blood cells as well as circulating immature myeloid cells. Although these findings are reported in the earlier literature, more modern reviews of the subject often fail to mention this association. We review the literature on these unusual manifestations of B12 deficiency and remind clinicians that splenomegaly and erythroblastosis can serve as diagnostic clues in cases of severe megaloblastic anemia secondary to B12 deficiency.

Publication Types:

- Case Reports

PMID: 18221385 [PubMed - indexed for MEDLINE]

Vitamin K1 and Bone Health

Nutr Res. 2009 Apr;29(4):221-8.

High-dose vitamin K supplementation reduces fracture incidence in postmenopausal women: a review of the literature.

Iwamoto J, **Sato Y**, **Takeda T**, **Matsumoto H**.

Institute for Integrated Sports Medicine, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8582, Japan. jiwamoto@sc.itc.keio.ac.jp

Although systematic review and meta-analysis of randomized controlled trials (RCTs) have concluded that vitamin K is effective in preventing fractures, the effect of vitamin K on the skeleton remains a matter of controversy. The objective of the present review of the literature was to evaluate the effect of vitamin K supplementation on the skeleton of postmenopausal women. PubMed was used to search the reliable literature for RCTs by using the search terms "vitamin K(1) or vitamin K(2)," "bone," and "postmenopausal women" and the following inclusion criteria: approximately 50 or more subjects per group and study period of 2 years or longer. Seven RCTs met the inclusion criteria. The results of these RCTs showed that vitamin K(1) and vitamin K(2) supplementation reduced serum undercarboxylated osteocalcin levels regardless of dose but that it had inconsistent effects on serum total osteocalcin levels and no effect on bone resorption. Despite the lack of a significant change or the occurrence of only a modest increase in bone mineral density, high-dose vitamin K(1) and vitamin K(2) supplementation improved indices of bone strength in the femoral neck and reduced the incidence of clinical fractures. The review of the reliable literature confirmed the effect of vitamin K(1) and vitamin K(2) supplementation on the skeleton of postmenopausal women mediated by mechanisms other than bone mineral density and bone turnover.

PMID: 19410972 [PubMed - in process]

Osteoporos Int. 2009 Jun;20(6):935-42. Epub 2008 Sep 30.

High prevalence of vitamin K and D deficiency and decreased BMD in inflammatory bowel disease.

Kuwabara A, **Tanaka K**, **Tsugawa N**, **Nakase H**, **Tsuji H**, **Shide K**, **Kamao M**, **Chiba T**, **Inagaki N**, **Okano T**, **Kido S**.

Department of Food and Nutrition, Kyoto Women's University, 35, Imakumano-kitahiyoshicho, Higashiyama, Kyoto 605-8501, Japan.

SUMMARY: Vitamin K and D deficiency and decreased bone mineral density (BMD) were highly prevalent in patients with inflammatory bowel disease (IBD), especially Crohn's disease (CD). Dietary intakes of these vitamins, however, were above the Japanese adequate intakes in IBD patients, suggesting that malabsorption is the basis for hypovitaminosis K and D and decreased BMD. INTRODUCTION: We have studied the possible involvement of vitamin K and D deficiency in the pathogenesis of decreased BMD in IBD. METHODS: Seventy patients with IBD were evaluated for their BMD; plasma levels of vitamin K; phylloquinone (PK), menaquinone-7 (MK-7), and 25OH-D; serum PTH, protein induced by vitamin K absence (PIVKA-II), and undercarboxylated osteocalcin (ucOC) levels; and their food intake. RESULTS: Compared with ulcerative colitis (UC) patients, CD patients had significantly lower plasma vitamin K and 25OH-D concentrations; significantly higher serum levels of PTH, PIVKA-II, and ucOC; and significantly lower BMD scores at almost all measurement sites. More IBD patients were vitamin K deficient in bone than in liver. Multiple regression analyses revealed that low plasma concentrations of vitamin K and 25OH-D were independent risk factors for low BMD and that they were associated with the patients' fat intake, but not with their intake of these vitamins. CONCLUSION: IBD patients have high prevalence of decreased BMD and vitamin K and D deficiency probably caused by malabsorption of these vitamins.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18825300 [PubMed - in process]

Proc Nutr Soc. 2008 May;67(2):163-76.

Importance of calcium, vitamin D and vitamin K for osteoporosis prevention and treatment.

Lanham-New SA.

Nutritional Sciences Division, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK. s.lanham-new@surrey.ac.uk

Throughout the life cycle the skeleton requires optimum development and maintenance of its integrity to prevent fracture. Bones break because the loads placed on them exceed the ability of the bone to absorb the energy involved. It is now estimated that one in three women and one in twelve men aged >55 years will suffer from osteoporosis in their lifetime and at a cost in the UK of > 1.7 pounds x 10(9) per year. The pathogenesis of osteoporosis is multifactorial. Both the development of peak bone mass and the rate of bone loss are determined by key endogenous and exogenous factors. Ca supplements appear to be effective in reducing bone loss in women late post menopause (>5 years post menopause), particularly in those with low habitual Ca intake (<400 mg/d). In women early post menopause (<5 years post menopause) who are not vitamin D deficient, Ca supplementation has little effect on bone mineral density. However, supplementation with vitamin D and Ca has been shown to reduce fracture rates in the institutionalised elderly, but there remains controversy as to whether supplementation is effective in reducing fracture in free-living populations. Re-defining vitamin D requirements in the UK is needed since there is evidence of extensive hypovitaminosis D in the UK. Low vitamin D status is associated with an increased risk of falling and a variety of other health outcomes and is an area that requires urgent attention. The role of other micronutrients on bone remains to be fully defined, although there are promising data in the literature for a clear link between vitamin K nutrition and skeletal integrity, including fracture reduction.

Publication Types:

- Review

PMID: 18412990 [PubMed - indexed for MEDLINE]

Arch Phys Med Rehabil. 2005 Mar;86(3):576-81.

Vitamin K deficiency and osteopenia in elderly women with Alzheimer's disease.

Sato Y, Honda Y, Hayashida N, Iwamoto J, Kanoko T, Satoh K.

Department of Neurology, Mitate Hospital, Tagawa, Japan. y-sato@ktarn.or.jp

OBJECTIVE: To analyze the relation between vitamin K status and bone mineral density (BMD) in women with Alzheimer's disease (AD). DESIGN: Cross-sectional study. SETTING: Outpatient departments of neurology and neuropsychiatry at a hospital in Japan. Participants One hundred women with AD (mean age, 79.8 y) and 100 age-matched community dwelling controls (mean age, 80.6 y). INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Patients were divided into 2 groups according to the degree of dementia: the mild AD group was composed of patients with a score in Mini-Mental State Examination (MMSE) of 16 and above (n=42); patients in the severe AD group had MMSE scores below 15 (n=58). We assessed body mass index (BMI). BMD was measured by computed x-ray densitometry. Serum concentrations of vitamin K 1 , 25-hydroxyvitamin D (25[OH]D 3), intact parathyroid hormone (PTH), and Glu osteocalcin (OC) were measured. RESULTS: BMI was significantly lower in women with more severe AD. Metacarpal BMD (P <.02) and serum concentrations of vitamin K 1 (P <.03) and 25(OH)D 3 (P <.001) were significantly lower in the severe AD group than in the mild AD group. Serum levels of intact PTH and Glu OC in severely demented patients were higher than those with mild dementia (P <.001). Serum PTH concentration correlated negatively with serum 25(OH)D 3 level (r =-.241, P =.016). Serum concentration of vitamin K 1 correlated positively with that of 25(OH)D 3 (r =.423, P <.001) and MMSE score (r =.353, P <.001), and negatively with Glu OC (r =-.580, P <.001). CONCLUSIONS: In female AD patients, nutritional vitamin K 1 deficiency may reduce production of fully carboxylated OC, which in turn may cause reduced BMD. Lower BMIs in more severe AD may imply the presence of general malnutrition in such a patient group.

PMID: 15759247 [PubMed - indexed for MEDLINE]

Int J Artif Organs. 2009 Feb;32(2):67-74.

Coagulation meets calcification: the vitamin K system.

Krueger T, **Westenfeld R**, **Schurgers L**, **Brandenburg V**.

Department of Nephrology and Clinical Immunology, University Hospital of the RWTH Aachen, Aachen - Germany.

Morbidity and mortality are massively increased in patients with chronic kidney disease (CKD) and patients with end-stage renale disease (ESRD). Bone disease (renal osteodystrophy) and vascular disease (accelerated arteriosclerosis) are two typical entities contributing to this excess morbidity and mortality. Vitamin K and vitamin K-dependent-proteins play pivotal roles in the physiology of mineralization and in preventing ectopic calcification: two of these vitamin K-dependent-proteins are osteocalcin (regulating bone mineralization) and matrix-Gla protein (MGP, local calcification inhibitor in the vessel wall). Vitamin K deficiency impairs the physiological function of osteocalcin and MGP and, therefore, presumably contributes to bone demineralisation and vascular calcification (the so-called calcification paradox). In this context, the usage of vitamin K antagonists for long-term oral anticoagulation therapy might be risky especially in CKD patients exhibiting a high background level of vascular calcification. We present a summary of data describing the potential role of vitamin K deficiency and supplementation in bone and vascular disease in patients with CKD or ESRD.

PMID: 19363777 [PubMed - in process]

Am J Clin Nutr. 2008 Aug;88(2):356-63.

Vitamin K, circulating cytokines, and bone mineral density in older men and women.

Shea MK, **Dallal GE**, **Dawson-Hughes B**, **Ordovas JM**, **O'Donnell CJ**, **Gundberg CM**, **Peterson JW**, **Booth SL**.

US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA.

BACKGROUND: Vitamin K modulates cytokines involved in bone turnover, including interleukin-6 (IL-6) and osteoprotegerin in vitro. OBJECTIVE: The objective of this study was to assess 1) associations between measures of vitamin K status [plasma phylloquinone and serum percentage of undercarboxylated osteocalcin (%ucOC)] and IL-6, osteoprotegerin, and C-reactive protein (CRP) concentrations and 2) the effect of daily 500 mug phylloquinone supplementation for 3 y on cytokine concentrations. DESIGN: Concentrations of IL-6, osteoprotegerin, and CRP and bone mineral density (BMD) were measured at baseline and after 3 y of follow-up in 379 healthy men and women (60-81 y; 58.5% women) participating in a randomized trial that studied the effect of vitamin K supplementation on bone loss. RESULTS: Cross-sectionally, plasma phylloquinone was inversely associated with IL-6 and CRP, whereas serum %ucOC was inversely associated with IL-6. Osteoprotegerin was associated positively with plasma phylloquinone and inversely with %ucOC. No differences were observed in the 3-y change in IL-6, osteoprotegerin, and CRP concentrations between participants who received phylloquinone supplementation and those who did not. Overall, no association was observed between the 3-y changes in circulating cytokines and BMD. CONCLUSIONS: Poor vitamin K status was associated with high concentrations of cytokines involved in bone turnover, but vitamin K supplementation did not confer a decrease in cytokine concentrations. The healthy status of this cohort may explain a lack of effect of vitamin K supplementation on cytokine concentrations. This trial was registered with www.clinicaltrials.gov as NCT00183001.

PMID: 18689371 [PubMed - indexed for MEDLINE]

Clin Exp Rheumatol. 2008 May-Jun;26(3):484-91.

Extremes in vitamin K status of bone are related to bone ultrasound properties in children with juvenile idiopathic arthritis.

van Summeren MJ, **Vermeer C**, **Engelbert RH**, **Schurgers LJ**, **Takken T**, **Fischer K**, **Kuis W**.

Department of Paediatric Immunology, University Medical Centre Utrecht, The Netherlands. m.j.h.vansummeren@umcutrecht.nl

OBJECTIVE: Osteopenia is a common complication of juvenile idiopathic arthritis (JIA). In adults, low bone density and increased fracture risk are associated with low vitamin K status of bone. The vitamin K-dependent protein osteocalcin plays an important role in bone metabolism. Its activity depends upon post-translational carboxylation in which vitamin K is an essential co-factor. Hence, vitamin K deficiency leads to under-carboxylated (i.e., inactive) osteocalcin (ucOC). Little is known about the vitamin K status and bone health in children with juvenile idiopathic arthritis (JIA). We studied the vitamin K status of bone and its association with bone mass properties in children with JIA compared to healthy children. METHODS: We performed a cross sectional study in 55 children with JIA and 54 healthy controls between 6-18 years of age. Bone markers, ultrasound bone mass properties and vitamin K status of bone were determined. RESULTS: Overall, no differences in vitamin K status of bone were found between the study groups. Among children with JIA, a high ratio of ucOC/cOC indicating low vitamin K status was associated with low bone ultrasound parameters, whereas children with a high vitamin K status had markedly higher bone properties. This association was independent of physical activity, age, gender and BMI. CONCLUSION: These results suggest that vitamin K may be one of multiple risk factors for low bone mass in children with JIA, in addition to other recognized determinants of bone mass. The question remains whether JIA patients would benefit from increased dietary vitamin K intake.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18578975 [PubMed - indexed for MEDLINE]

Vitam Horm. 2008;78:417-34.

Diagnosis of osteoporosis with vitamin k as a new biochemical marker.

Heiss C, **Hoesel LM**, **Wehr U**, **Wenisch S**, **Drosse I**, **Alt V**, **Meyer C**, **Horas U**, **Schieker M**, **Schnettler R**.

Department of Trauma Surgery, University Hospital of Giessen-Marburg, Giessen, Germany.

Osteoporosis is a metabolic bone disease characterized by reduced bone quality and quantity. As a consequence, patients are at risk for fractures, subsequent immobility, and higher mortality especially among elder patients. Because of the high incidence of complications and the associated financial burden for the health system, new parameters for diagnostic and therapeutic purposes are urgently needed. In this regard, research focused on vitamin K as a biochemical bone marker has provided promising results. Vitamin K represents an important enzyme-cofactor for the posttranslational modification and activation of several proteins involved in bone metabolism. Vitamin K has been proven to be a valuable diagnostic as well as therapeutic parameter especially in osteoporosis. Patients with osteoporosis have been shown to have decreased levels of vitamin K. Further, regular intake of vitamin K may increase bone mineral density (BMD), thereby lowering the fracture risk. Yet vitamin K alone may not sufficiently indicate the mineral status of the bone. However, the usefulness of a combination of several biochemical bone markers as improved surrogate markers of bone metabolism has been shown recently. Therefore, this review will focus on the significance and importance of vitamin K for bone metabolism. Beyond this, aspects on the current and prospective use of vitamin K as well as other newly developed biochemical bone markers will be discussed.

Publication Types:

- Review

PMID: 18374203 [PubMed - indexed for MEDLINE]

Vitam Horm. 2008;78:393-416.

Vitamin K and bone health in adult humans.

Bügel S.

Department of Human Nutrition, University of Copenhagen, Rolighedsvej 30, DK-1958 Frederiksberg C, Denmark.

Vitamin K is receiving more attention in relation to its role in bone metabolism. Vitamin K is a coenzyme for glutamate carboxylase, which mediates the conversion of glutamate to gamma-carboxyglutamate (Gla). The gamma-carboxylation of the Gla proteins is essential for the proteins to attract Ca2+ and to incorporate these into hydroxyapatite crystals. The best known of the three known bone-related Gla proteins is osteocalcin (OC). Even though the exact role of OC is not known, a number of studies have shown that vitamin K insufficiency or high levels of undercarboxylated osteocalcin (ucOC) is associated with an increase in the concentration of circulating ucOC. Furthermore, several studies have demonstrated that vitamin K insufficiency is associated with low bone mineral density (BMD) and increased fractures. Vitamin K supplementation, on the other hand, has been shown to improve the bone turnover profile and decrease the level of circulating ucOC. Dietary recommendations are based on saturation of the coagulation system, and in most countries the dietary intake is sufficient to obtain the amount recommended. In relation to bone, requirements might be higher. The aim of this chapter is to give an overview of the importance of vitamin K in relation to bone health in adult humans and thereby in the prevention of osteoporosis. Furthermore, I will shortly discuss the interaction with vitamin D and the paradox in relation to warfarin treatment.

Publication Types:

- Review

PMID: 18374202 [PubMed - indexed for MEDLINE]

Br J Nutr. 2008 Oct;100(4):852-8. Epub 2008 Feb 18.

Vitamin K status is associated with childhood bone mineral content.

van Summeren MJ, **van Coeverden SC**, **Schurgers LJ**, **Braam LA**, **Noirt F**, **Uiterwaal CS**, **Kuis W**, **Vermeer C**.

Department of Paediatric Immunology, University Medical Centre Utrecht, PO Box 85090, Utrecht, The Netherlands. m.j.h.vansummeren@umcutrecht.nl

In adult bone, vitamin K contributes to bone health, probably through its role as co-factor in the carboxylation of osteocalcin. In children, the significance of vitamin K in bone-mass acquisition is less well known. The objective of this longitudinal study was to determine whether biochemical indicators of vitamin K status are related to (gains in) bone mineral content (BMC) and markers of bone metabolism in peripubertal children. In 307 healthy children (mean age 11.2 years), BMC of the total body, lumbar spine and femoral neck was determined at baseline and 2 years later. Vitamin K status (ratio of undercarboxylated (ucOC) to carboxylated (cOC) fractions of osteocalcin; UCR) was also measured at both time points. Markers of bone metabolism, sex steroids, vitamin D status and growth hormones were measured at baseline only. Large variations in the levels of the UCR were found at both time-points, indicating a substantial interindividual difference in vitamin K status. Improvement of vitamin K status over 2 years (n 281 children) was associated with a marked increase in total body BMC (r -49.1, P<0.001). The UCR was associated with pubertal stage, markers of bone metabolism, sex hormones and vitamin D status. A better vitamin K status was associated with more pronounced increase in bone mass in healthy peripubertal children. In order to determine the significance of these findings for childhood bone health, additional paediatric studies are needed.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18279558 [PubMed - indexed for MEDLINE]

Mayo Clin Health Lett. 2007 Nov;25(11):4.

Vitamin K linked to bone strength.

[No authors listed]

Publication Types:

- News

PMID: 18232068 [PubMed - indexed for MEDLINE]

J Endocrinol Invest. 2007;30(6 Suppl):24-8.

Role of vitamin K on biochemical markers, bone mineral density, and fracture risk.

Francucci CM, **Rilli S**, **Fiscaletti P**, **Boscaro M**.

Division of Endocrinology, Department of Internal Medicine, Polytechnic University of Marche, Ancona, Italy. cm.francucci@ao-umbertoprimo.marche.it

Osteoporosis is a multifactorial chronic disease that may become even more prevalent and more of a public health problem in the decades to come. Recent research has indicated that a number of macro- and micronutrients are involved in the development of bone health. In the past decade it became evident that vitamin K played a significant role in human health beyond its well-established function in blood clotting. In fact, among the proteins known or suspected to be involved in bone and vascular biology there are several members of the vitamin K dependent or gamma-carboxyglutamic acid protein family. Based on the current evidence from epidemiologic and intervention studies, there are insufficient data to recommend a routine supplementation of vitamin K for optimal bone health. New experimental and placebo-controlled studies in humans should clarify our understanding of the role vitamin K plays in improving bone health.

Publication Types:

- Review

PMID: 17721070 [PubMed - indexed for MEDLINE]

Clin Calcium. 2007 Nov;17(11):1717-26.

[Serum vitamin K concentration and nutrition]

[Article in Japanese]

Tsugawa N, **Okano T**.

Kobe Pharmaceutical University, Department of Hygienic Sciences.

Vitamin K (VK) is well known for its role in the synthesis of a number of blood coagulation factors. VK is also an important factor for bone metabolism via gamma-carboxylation of VK-dependent proteins such as osteocalcin, matrix Gla protein, and protein S. Recently, it is rare that severe VK deficiency is observed. However, low dietary VK intake or low VK status has been shown to be associated with low bone mineral density and increased hip fracture risk. These studies suggest that there is potential VK insufficiency in bone, even in sufficient VK status for blood coagulation. In the present review, the studies concerning relationship between serum VK concentration and bone health, including pharmacokinetics of VK analogues (such as phylloquinone and menaquinone) and factors which affect on blood circulation of VK, are reviewed.

Publication Types:

- English Abstract
- Review

PMID: 17982192 [PubMed - indexed for MEDLINE]

Int J Vitam Nutr Res. 2006 Nov;76(6):385-90.

A preliminary assessment of vitamin K1 intakes and serum undercarboxylated osteocalcin levels in 11-13 year old Irish girls.

Collins A, **Cashman KD**, **Kiely M**.

Department of Food and Nutritional Sciences, University College, Cork, Ireland. collinsaoife@ucc.ie

Low vitamin K1 intakes have been associated with low bone mineral density in women and reduced bone turnover in girls. No European data exist on the relationship between vitamin K1 and serum undercarboxylated osteocalcin (ucOC), an indicator of K1 status in adolescents. The aim of the current study was to assess intakes of vitamin K1 in relation to serum ucOC status in Irish girls. A detailed dietary history method, which measured habitual intakes from a typical 14-day period, was used to estimate vitamin K1 intakes in 18 girls aged 11-13 years. Recently compiled and validated food composition data for vitamin K1 were used to determine vitamin K1 intakes. An enzyme immunoassay was used to measure ucOC in fasting serum samples. The mean (+/- SD) intake of vitamin K1 in the girls was 72.4 microg/day (SD 34.4). Vegetables (particularly broccoli, composite dishes, and lettuce) contributed 53% of total vitamin K1 intakes. Thirty-Seven percent of the girls failed to meet the current U.S. adequate intake for adolescents of 60 microg/day vitamin K1. Serum ucOC levels were inversely related to body weight-adjusted vitamin K1 intakes, controlling for energy intake (partial correlation r = -0.538; p = 0.026). The data indicate that large-scale studies to examine relationships between vitamin K1 (and green vegetable) intakes and bone growth and development in adolescents are warranted.

PMID: 17607958 [PubMed - indexed for MEDLINE]

Med Monatsschr Pharm. 2007 Jan;30(1):35-6.

[Vitamin K for prevention of fracture]

[Article in German]

Ecker-Schlipf B.

PMID: 17262902 [PubMed - indexed for MEDLINE]

Nippon Rinsho. 2006 Sep;64(9):1639-43.

[Active vitamin D and vitamin K as therapeutic agents for osteoporosis]

[Article in Japanese]

Katagiri H.

Department of Orthopaedic Surgery, Medicine of Sensory and Motor Organs, Faculty of Medicine, Tottori University.

Active vitamin D has been most widely used in Japan for the treatment of osteoporosis. However, clinical evidence for its efficacy as an anti-osteoporotic drug is scarce in terms of fracture prevention. Recent reports suggest that active vitamin D may prevent fracture not only through enhancement of intestinal calcium absorption but also by improving bone quality and/or strength independently of bone mass and by improving neuromuscular function to reduce the number of fall. Low serum concentrations of vitamin K have been reported in patients with osteoporosis, and serum osteocalcin appears to be undercarboxylated in these individuals, a process dependent on vitamin K. Undercarboxylated osteocalcin is also a significant risk for hip fracture. Clinical studies in Japan suggest that menatetrenone (vitamin K2) reduces skeletal losses and, in a small randomized clinical trial, it reduced the rate of vertebral fractures. Menatetrenone is currently used in Japan, the Republic of Korea and Thailand.

Publication Types:

- English Abstract
- Review

PMID: 16972672 [PubMed - indexed for MEDLINE]

Clin Calcium. 2006 Sep;16(9):1526-34.

[Protective effects of vitamin K against osteoporosis and its pleiotropic actions]

[Article in Japanese]

Kaneki M.

Harvard Medical School, Massachusetts General Hospital, Department of Anesthesia & Critical Care.

Vitamin K is a nutrient originally identified as an essential factor for blood coagulation. Recently, vitamin K has emerged as a potential protector against osteoporosis and hepatocarcinoma. Accumulated evidence indicates that subclinical non-hemostatic vitamin K deficiency in extrahepatic tissues, particularly in bone, exists widely in the otherwise healthy adult population. Both vitamin K(1) and K(2) have been shown to exert protective effects against osteoporosis. Moreover, therapeutic potential of vitamin K(2) as an anti-hepatoma drug has been recently highlighted. Most of the new biological functions of vitamin K in bone and hepatoma cells are considered to be attributable to promotion of gamma-carboxylation of glutamic acid residues in vitamin K-dependent proteins, which is shared by both vitamins K(1) and K(2). In contrast, vitamin K(2)-specific, gamma-carboxylation-unrelated functions have also been demonstrated. These functions include stimulation of steroid and xenobiotic receptor (SXR)-mediated transcription and anti-oxidant property. Thus, biological differences between vitamins K(1) and K(2), and a potential involvement of gamma-carboxylation-independent actions in the new roles of vitamin K remain open issues. Molecular bases of coagulation-unrelated pleiotropic actions of vitamin K and its implications in human health deserve further investigations.

Publication Types:

- English Abstract
- Review

PMID: 16951479 [PubMed - indexed for MEDLINE]

Arch Intern Med. 2006 Jun 26;166(12):1256-61.

Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials.

Cockayne S, **Adamson J**, **Lanham-New S**, **Shearer MJ**, **Gilbody S**, **Torgerson DJ**.

York Trials Unit, Department of Health Sciences, University of York, York YO10 5DD, England. djt6@york.ac.uk

BACKGROUND: Observational and some experimental data suggest that low intake of vitamin K may be associated with an increased risk of fracture. OBJECTIVE: To assess whether oral vitamin K (phytonadione and menaquinone) supplementation can reduce bone loss and prevent fractures. DATA SOURCES: The search included the following electronic databases: MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), the Cochrane Library (issue 2, 2005), the ISI Web of Science (1945 to June 2005), the National Research Register (inception to the present), Current Controlled Trials, and the Medical Research Council Research Register. STUDY SELECTION: Randomized controlled trials that gave adult participants oral phytonadione and menaquinone supplements for longer than 6 months were included in this review. DATA EXTRACTION: Four authors extracted data on changes in bone density and type of fracture. All articles were double screened and double data extracted. DATA SYNTHESIS: Thirteen trials were identified with data on bone loss, and 7 reported fracture data. All studies but 1 showed an advantage of phytonadione and menaquinone in reducing bone loss. All 7 trials that reported fracture effects were Japanese and used menaquinone. Pooling the 7 trials with fracture data in a meta-analysis, we found an odds ratio (OR) favoring menaquinone of 0.40 (95% confidence interval [CI], 0.25-0.65) for vertebral fractures, an OR of 0.23 (95% CI, 0.12-0.47) for hip fractures, and an OR of 0.19 (95% CI, 0.11-0.35) for all nonvertebral fractures. CONCLUSIONS: This systematic review suggests that supplementation with phytonadione and menaquinone-4 reduces bone loss. In the case of the latter, there is a strong effect on incident fractures among Japanese patients.

Publication Types:

- Meta-Analysis
- Review
- PMID: 16801507 [PubMed - indexed for MEDLINE]

Vitamin K1 and Blood Improvement

J Perinat Med. 2006;34(2):173-6.

Maternal antenatal administration of vitamin K1 results in increasing the activities of vitamin K-dependent coagulation factors in umbilical blood and in decreasing the incidence rate of periventricular-intraventricular hemorrhage in premature infants.

Liu J, **Wang Q**, **Gao F**, **He JW**, **Zhao JH**.

Department of Neonatology, Beijing Obstetrics and Gynecology Hospital, Affiliated to Capital University of Medical Science, China. liuzhuokun@hotmail.com

AIMS: Infants less than 35 weeks' gestation age are susceptible to periventricular-intraventricular hemorrhage (PIVH). This may be partially attributable to low concentrations of vitamin K-dependent coagulation factors. The purposes of this study were: (1) to determine the umbilical blood activity levels of vitamin K-dependent coagulation factors II, VII, IX and X; (2) to investigate the change in activities of these factors in premature infants' umbilical blood after prenatal administration of vitamin K1 to the mothers; and (3) to study the prophylactic effects on PIVH after maternal antenatal supplemental vitamin K1. METHODS: Pregnant women in preterm labor at less than 35 weeks of gestation were randomly selected to receive antenatal vitamin K1 10 mg per day injection intramuscularly or intravenously for 2-7 days (vitamin K1 group, n = 40), or no such treatment (control group, n = 50). At the same period, cord blood samples were collected from thirty full-term neonates to compare the factor levels with those of premature infants. Intracranial ultrasound was performed by the same sonographer to determine the presence and severity of PIVH. RESULTS: The activities of vitamin K-dependent coagulation factors in umbilical blood in the control group were: factor II 25.64+/-9.49%, factor VII 59.00+/-17.66%, factor IX 24.67+/-8.88%, and factor X 30.16+/-5.02%. In full-term infants, the respective values were: factor II 36.70+/-4.88%, factor VII 64.54+/-10.62%, factor IX 30.18+/-5.69%, and factor X 34.32+/-12.63%. In vitamin K1 group these factors were: factor II 36.35+/-6.88%, factor VII 69.59+/-16.55%, factor IX 25.71+/-10.88%, and factor X 39.26+/-8.02%. The data suggest the absence of vitamin K-dependent coagulation factors in preterm infants, and antenatal supplement of vitamin K1 may increase the cord blood activity of factor II, VII and factor X ($P < 0.001$). In addition, the overall rates of PIVH in the vitamin K1 group and in controls were 32.4 and 52.0%, respectively ($P = 0.036$), and the frequency of severe PIVH was 5.0 and 20.0%, respectively ($P = 0.038$). CONCLUSIONS: Administration of vitamin K1 to pregnant women at less than 35 weeks' gestation age may result in improved coagulation and may reduce the incidence as well as the severity degree of PIVH.

PMID: 16519625 [PubMed - indexed for MEDLINE]

Eur J Nutr. 2004 Dec;43(6):325-35. Epub 2004 Feb 5.

Beyond deficiency: potential benefits of increased intakes of vitamin K for bone and vascular health.

Vermeer C, **Shearer MJ**, **Zittermann A**, **Bolton-Smith C**, **Szulc P**, **Hodges S**, **Walter P**, **Rambeck W**, **Stöcklin E**, **Weber P**.

Dept. of Biochemistry, University of Maastricht, P. O. Box 616, 6200 MD Maastricht, The Netherlands. c.vermeer@bioch.unimaas.nl

Vitamin K is well known for its role in the synthesis of a number of blood coagulation factors. During recent years vitamin K-dependent proteins were discovered to be of vital importance for bone and vascular health. Recommendations for dietary vitamin K intake have been made on the basis of the hepatic requirements for the synthesis of blood coagulation factors. Accumulating evidence suggests that the requirements for other functions than blood coagulation may be higher. This paper is the result of a closed workshop (Paris, November 2002) in which a number of European vitamin K experts reviewed the available data and formulated their standpoint with respect to recommended dietary vitamin K intake and the use of vitamin K-containing supplements.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 15309455 [PubMed - indexed for MEDLINE]

Arch Dis Child Fetal Neonatal Ed. 2004 Nov;89(6):F546-50.

Intracranial haemorrhage due to late onset vitamin K deficiency bleeding in Hanoi province, Vietnam.

Danielsson N, **Hoa DP**, **Thang NV**, **Vos T**, **Loughnan PM**.

Astrid Lindgren's Children's Hospital, Stockholm, Sweden.

BACKGROUND: In many developing countries vitamin K prophylaxis is not routinely administered at birth. There are insufficient data to assess the cost effectiveness of its implementation in such countries. OBJECTIVE: To estimate the burden of intracranial haemorrhage caused by late onset vitamin K deficiency bleeding in Hanoi, Vietnam. METHODS: Cases of intracranial haemorrhage in infants aged 1-13 weeks were identified in Hanoi province for 5 years (1995-1999), and evidence for vitamin K deficiency was sought. The data were compared with those on vitamin K deficiency bleeding in developed countries and used to obtain an approximation to the incidence of intracranial haemorrhage caused by vitamin K deficiency bleeding in Hanoi. RESULTS: The estimated incidence of late onset vitamin K deficiency bleeding in infants who received no prophylaxis was unexpectedly high (116 per 100,000 births) with 142 and 81 per 100,000 births in rural and urban areas respectively. Mortality was 9%. Of the surviving infants, 42% were neurologically abnormal at the time of hospital discharge. Identified associations were rural residence, male sex, and low birth weight. A significant reduction in the incidence was observed in urban Hanoi during 1998 and 1999, after vitamin K prophylaxis was introduced at one urban obstetric hospital. CONCLUSIONS: Vitamin K deficiency bleeding is a major public health problem in Hanoi. The results indicate that routine vitamin K prophylaxis would significantly reduce infant morbidity and mortality in Vietnam and, costing an estimated 87 US dollars (48 pounds, 72 Euro) per disability adjusted life year saved, is a highly cost effective intervention.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15499152 [PubMed - indexed for MEDLINE]

PMCID: PMC1721780

Pediatr Blood Cancer. 2009 Jul;53(1):92-5.

Novel splice site mutations in the gamma glutamyl carboxylase gene in a child with congenital combined deficiency of the vitamin K-dependent coagulation factors (VKCFD).

Titapiwatanakun R, **Rodriguez V**, **Middha S**, **Dukek BA**, **Pruthi RK**.

Division of Pediatric Hematology Oncology, Mayo Clinic, Rochester, Minnesota 55905, USA.

Congenital combined deficiency of the vitamin K-dependent coagulation factors is a rare bleeding disorder caused by either a defect in the gamma-glutamyl carboxylase or the vitamin K epoxide reductase enzyme complex. The diagnosis should be considered when vitamin-K dependent factor activities are decreased and liver dysfunction, vitamin K deficiency, and factitious coumarin ingestion have been excluded. We report a case of VKCFD in a child resulting from compound heterozygosity for two novel splice site mutations of the gamma-glutamyl carboxylase gene. Oral vitamin K supplementation resulted in partial resolution of proteins and complete resolution of bleeding.

Publication Types:

- Case Reports

PMID: 19340858 [PubMed - indexed for MEDLINE]

Thromb Haemost. 2009 Feb;101(2):410-1.

An oral vitamin K protocol to reverse over-anticoagulation in patients presenting with an International Normalised Ratio above 10.0.

Denas G, **Cucchini U**, **Iliceto S**, **Pengo V**.

Clinical Cardiology, Thrombosis Centre, Via Giustiniani 2, 35128 Padova, Italy.

Publication Types:

- Letter

PMID: 19190831 [PubMed - indexed for MEDLINE]

Eur J Pediatr. 2009 Feb;168(2):127-34. Epub 2008 Nov 4.

Vitamin K, an update for the paediatrician.

Van Winckel M, **De Bruyne R**, **Van De Velde S**, **Van Biervliet S**.

Department of Paediatrics, UZ Gent, De Pintelaan 185, 9000 Ghent, Belgium. myriam.vanwinckel@ugent.be

INTRODUCTION: This review summarizes current knowledge on vitamin K for the paediatrician. Vitamin K is a fat-soluble vitamin, present in plants as phylloquinone and produced by bacteria as menaquinone. It is acting as a co-factor for gamma-glutamyl carboxylase. This enzyme is responsible for post-translational modification of some glutamate side chains to gamma-carboxyglutamate. The majority of gamma-carboxylated proteins function in blood coagulation; others play a role in calcium homeostasis. DATA: Newborn babies are at particular risk of vitamin K deficiency, as placental transfer is limited and human milk is a poor source. Vitamin K prophylaxis at birth effectively prevents vitamin K deficiency bleeding (VKDB), formerly known as "haemorrhagic disease of the newborn". Recent epidemiological studies provide data on the effectiveness of different administration routes and dosing schemes. Infants of mothers taking drugs that inhibit vitamin K are at risk of early VKDB and should receive 1 mg intramuscular (i.m.) as soon as possible after birth. Classic VKDB is prevented by intramuscular as well as by oral administration of 1 mg vitamin K. In exclusively breast-fed infants, single i.m. administration at birth is also effectively preventing (rare) late VKDB but single oral administration is not. If given orally, prophylaxis should be continued by either weekly administration of 1 mg till 12 weeks or repeating 2 mg at weeks 1 and 4. Daily administration of 25 microg offers insufficient protection. The only infants not fully protected in this way are those with yet unrecognised liver disease. CONCLUSIONS: Further work is needed before firm recommendations can be made regarding dose in preterm infants and in patients with fat malabsorption/cholestasis or regarding the role of vitamin K in the prevention of osteoporosis.

Publication Types:

- Review

PMID: 18982351 [PubMed - indexed for MEDLINE]

Vitamin K1 and Blood Improvement

Wien Med Wochenschr. 2008;158(13-14):385-95.

The neonatal coagulation system and the vitamin K deficiency bleeding - a mini review.

Pichler E, **Pichler L**.

Department of Paediatrics, Landeskrankenhaus Klagenfurt, Klagenfurt, Austria.

Coagulation factors do not cross the placental barrier but are synthesized independently by the conceptus. At birth, activities of the vitamin K dependent factors II, VII, IX, and X and the concentrations of the contact factors XI and XII are reduced to about 50% of normal adult values. The levels of the factors V, VIII, XIII, and fibrinogen are similar to adult values. Plasma concentrations of the naturally occurring anticoagulant proteins (antithrombin, protein C, and protein S) are significantly lower at birth than during the adult years. Plasminogen is reduced by approximately 50%. Platelet counts are within the normal range, regarding function, however, neonatal platelets seem to be hyporeactive. The von Willebrand factor contains large multimers and its concentration is increased. Properties and functions of vitamin K as well as requirement and plasma concentrations in newborns are reviewed. Regarding vitamin K deficiency bleeding (VKDB), the classical nomenclature is used: "early" (presenting within the first 24 h of life), "classical" (day 1-7 after birth), and "late" (8 days to 6 months). After the presentation of the history of vitamin K prophylaxis, vitamin K levels are described as can be expected after the administration of prophylactic doses at various routes. Subsequently, the actual schedule of vitamin K prophylaxis as recommended by the "Osterreichische Gesellschaft für Kinder- und Jugendheilkunde" is given as follows: i) the oral treatment of healthy full-term babies and orally fed preterm babies, ii) the parenteral treatment of small preterm and sick full-term babies, and iii) the treatment of mothers under medication with enzyme-inducing drugs with vitamin K during the last 15-30 days of pregnancy. The regimes of prophylactic vitamin K treatment of different countries are also given. Finally, the therapeutic use of vitamin K is addressed; the potential use of fresh-frozen plasma, prothrombin complex preparations, and recombinant factor VIIa is discussed.

Publication Types:

- Comparative Study
- Review

PMID: 18677590 [PubMed - indexed for MEDLINE]

J Toxicol Sci. 2008 Aug;33(3):307-14.

Blood coagulation-related parameter changes in Sprague-Dawley (SD) rats treated with phenobarbital (PB) and PB plus vitamin K.

Mochizuki M, **Shimizu S**, **Kitazawa T**, **Umeshita K**, **Goto K**, **Kamata T**, **Aoki A**, **Hatayama K**.

Toxicology Department, Gotemba Laboratory, Bozo Research Center Inc., Shizuoka. mochizuki@bozo.co.jp

Effects of dose and duration of phenobarbital (PB) administration and those of co-administration of PB and vitamin K on blood coagulation-related parameters were examined in specific pathogen-free (SPF) rats of Sprague-Dawley strain kept on an ordinary diet. In Experiment 1, oral administration of PB (0, 25, 50, 100 or 150 mg/kg/day) for 2 weeks induced increases in hepatic cytochrome P450 content and CYP2B expression, prolongation of coagulation time (activated partial thromboplastin time (APTT) and Thrombotest (TBT)) and an increase in anti-thrombin III (AT III) concentration in a dose-dependent manner. In Experiment 2, PB administration (100 mg/kg/day) for up to 14 days produced time-dependent increases in hepatic cytochrome P450 content and CYP2B (CYP2B1 and CYP2B2) expression. APTT was prolonged from day 1 and AT III concentration was increased from day 2, whereas the coagulation time (TBT) was prolonged from day 7. In Experiment 3, APTT prolonged by PB (100 mg/kg/day) was shortened after vitamin K(2) (30 mg/kg/day) co-administration, although AT III concentration was still increased. This suggests that not AT III but PB-induced vitamin K deficiency may play an important role in PB-induced prolongation of coagulation time in SPF rats kept on an ordinary diet.

PMID: 18670162 [PubMed - indexed for MEDLINE]

Vitam Horm. 2008;78:265-79.

Vitamin K and thrombosis.

Merli GJ, **Fink J**.

Professor of Medicine, Director Jefferson Center for Vascular Diseases, Jefferson Medical College, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA.

Vitamin K was discovered in the 1930s during cholesterol metabolism experiments in chickens. It is a fat-soluble vitamin which occurs naturally in plants as phylloquinone (vitamin K1) and is produced by gram-negative bacteria in the human gastrointestinal tract as menaquinone (vitamin K2). This vitamin was found to be essential for normal functioning of hemostasis. In addition, a number of clinical conditions in which vitamin K deficiency was found to be the underlying pathophysiologic problem were discovered. These conditions include hemorrhagic disease of the newborn, obstructive jaundice, and malabsorption syndromes. The importance of this vitamin has become more apparent with the discovery of the anticoagulant warfarin which is a vitamin K antagonist. There are millions of patients on this therapy for a variety of thrombogenic conditions such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, and prosthetic cardiac valves. The wide use of this narrow therapeutic index drug has resulted in significant risk for major bleeding. Vitamin K serves as one of the major reversing agent for patients over-anticoagulated with warfarin. In the past few years, research has focused on new areas of vitamin K metabolism, which include bone and endovascular metabolism; cell growth, regulation, migration, and proliferation; cell survival, apoptosis, phagocytosis, and adhesion. These new areas of research highlight the significance of vitamin K but raise new clinical questions for patients who must be maintained on long-term warfarin therapy.

Publication Types:

- Review

PMID: 18374199 [PubMed - indexed for MEDLINE]

Vitam Horm. 2008;78:227-46.

VKORC1: a warfarin-sensitive enzyme in vitamin K metabolism and biosynthesis of vitamin K-dependent blood coagulation factors.

Wallin R, **Wajih N**, **Hutson SM**.

Departments of Internal Medicine and Biochemistry, Wake Forest University School of Medicine, Winston-Salem, North Carolina 27157.

The recently discovered enzyme VKORC1 of the vitamin K cycle, which is the target for the anticoagulant drug warfarin, has opened new opportunities to understand warfarin resistance and biosynthesis of vitamin K-dependent blood coagulation factors and other members of this protein family. Furthermore, it has opened new opportunities to study the vitamin K-dependent posttranslational gamma-carboxylational system in the endoplasmic reticulum in greater detail and its molecular operation in vivo. Other accomplishments resulting from this discovery are: (1) the finding that VKORC1 is the rate-limiting step in biosynthesis of functional vitamin K-dependent proteins, and (2) engineering of recombinant intracellular gamma-carboxylation systems in cell lines producing recombinant coagulation factor used clinically to treat bleeding disorders. The engineered cells significantly enhance production of the fraction of fully functional gamma-carboxylated proteins compared to cell lines only overexpressing the specific coagulation factor. The first described inhibitor of the gamma-carboxylation system has been identified as calumenin, a resident chaperone in the endoplasmic reticulum (ER). Together, the new information gained about the vitamin K-dependent gamma-carboxylation system will stimulate new research which will benefit medicine and our understanding of the molecular mechanisms involved in this protein modification reaction.

Publication Types:

- Review

PMID: 18374197 [PubMed - indexed for MEDLINE]

Clin Calcium. 2007 Nov;17(11):1717-26.

[Serum vitamin K concentration and nutrition]

[Article in Japanese]

Tsugawa N, **Okano T**.

Kobe Pharmaceutical University, Department of Hygienic Sciences.

Vitamin K (VK) is well known for its role in the synthesis of a number of blood coagulation factors. VK is also an important factor for bone metabolism via gamma-carboxylation of VK-dependent proteins such as osteocalcin, matrix Gla protein, and protein S. Recently, it is rare that severe VK deficiency is observed. However, low dietary VK intake or low VK status has been shown to be associated with low bone mineral density and increased hip fracture risk. These studies suggest that there is potential VK insufficiency in bone, even in sufficient VK status for blood coagulation. In the present review, the studies concerning relationship between serum VK concentration and bone health, including pharmacokinetics of VK analogues (such as phylloquinone and menaquinone) and factors which affect on blood circulation of VK, are reviewed.

Publication Types:

- English Abstract
- Review

PMID: 17982192 [PubMed - indexed for MEDLINE]

Biosci Biotechnol Biochem. 2006 Apr;70(4):926-32.

Vitamin K suppresses lipopolysaccharide-induced inflammation in the rat.

Ohsaki Y, **Shirakawa H**, **Hiwatashi K**, **Furukawa Y**, **Mizutani T**, **Komai M**.

Laboratory of Nutrition, Department of Science of Food Function and Health, Graduate School of Agricultural Science, Tohoku University , Sendai, Japan.

Vitamin K (K) is essential for blood coagulation and bone metabolism in mammals. K acts as a cofactor in the posttranslational synthesis of gamma-carboxyglutamic acid from glutamic acid residues. In addition to the liver and bone, K is found in the brain, heart, kidney and gonadal tissue. However, the physiological role of K in these various organs is not yet fully understood. It is likely that K has functions other than its role as a cofactor of protein gamma-glutamyl carboxylation. We used in this study the DNA microarray technique to identify the effect of K status on gene expression in the rat liver. The expression of genes involved in the acute inflammation response was enhanced in rats fed with a K-deficient diet relative to the control and K1-supplemented diet groups. Moreover, dietary supplementation with K1 suppressed the inflammation induced by lipopolysaccharide administration. These results indicate that orally administrated K1 suppressed inflammation in the rat.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 16636460 [PubMed - indexed for MEDLINE]

Blood Coagul Fibrinolysis. 2005 Oct;16(7):525-7.

Congenital vitamin K-dependent coagulation factor deficiency: a case report.

Bhattacharyya J, **Dutta P**, **Mishra P**, **Dixit A**, **Srinivas U**, **Kannan M**, **Kumar R**, **Choudhry VP**, **Saxena R**.

Department of Haematology, All India Institute of Medical Sciences, New Delhi, India.

Congenital vitamin K-dependent coagulation factor deficiency is a very rare bleeding disorder, which usually presents with episodes of intracerebral bleed in the first few weeks of life, sometimes leading to a fatal outcome. We report a case of combined factor deficiency of vitamin K-dependent factors in which the patient presented with both intracerebral bleeding, and possibly also thrombosis, and responded to a vitamin K supplement along with fresh frozen plasma.

Publication Types:

- Case Reports

PMID: 16175013 [PubMed - indexed for MEDLINE]

Clin Calcium. 2002 Aug;12(8):1123-8.

[Vitamin K and vascular calcification]

[Article in Japanese]

Shoji S.

Internal Medicine, Inoue Hospital.

Until recently, vitamin K has been exclusively related to blood coagulation. During the last decade, a second function for vitamin K-dependent proteins has become apparent : the regulation of tissue calcification. One of them is the function of Matrix Gla Protein (MGP) : potent inhibitors of vascular calcification. The function of MGP became clear from transgenic mice (MGP-deficient mice). Further research on MGP will resolve the complicated mechanism of atherosclerosis, especially of the arterial calcification. The recommended daily allowance for vitamin K to prevent vascular calcification should be evaluated.

Publication Types:

- English Abstract

PMID: 15775408 [PubMed]

JPEN J Parenter Enteral Nutr. 2004 Nov-Dec;28(6):388-98.

Observations on possible effects of daily vitamin K replacement, especially upon warfarin therapy.

Bern M.

Cancer Center of Boston, New England Baptist Hospital, Harvard Medical School, Boston, Massachusetts, USA. mbern@cancercenter.com

Daily parenteral vitamin K supplement is now recommended by the U.S. Food and Drug Administration (FDA) for patients receiving IV hyperalimentation. This is considered as preferable to the previous recommendations of weekly parenteral or oral supplement, or as in some cases no supplement at all. Supplemental vitamin K1 will ensure adequate supplies for hepatic saturation and thus the production of clotting factors II, VII, IX, and X, plus the anticoagulants protein C, protein S, and protein Z. But this is not the entire story. This recommended supplement will affect other physiologic systems that also use vitamin K-dependent gamma-carboxylation. Vitamin K is not 1 molecule but rather 2 natural substances, vitamin K1 and K2, and the synthetic K3's. It is not understood, what, if any, effect may occur because of the saturation or competition from the vitamin K1 upon the functioning of vitamins K2 and the derivatives of K3 in vivo upon bone mineralization, cell growth, and blood vessel health, all known to be influenced by the vitamins K. There are probably other physiologic systems yet to be studied relative to vitamins K and gamma-carboxylation. This review also considers the available research upon warfarin when given to patients receiving hyperalimentation and what effects the vitamin K supplements may have. Because studies to date have not controlled for vitamin K intake, consideration is given to whether one should expect any change in previously reported outcomes when using low-dose warfarin for prophylaxis against central vein thrombosis. Also considered are possible positive or negative effects that chronic warfarin therapy may have upon the other vitamin K-dependent systems under discussion. This review offers a platform for further discussion and derived clinical research provoked by this new FDA recommendation.

Publication Types:

- Review

PMID: 15568285 [PubMed - indexed for MEDLINE]

Haemophilia. 2004 Oct;10 Suppl 4:188-95.

Acquired bleeding disorders: the impact of health problems in the developing world.

Isarangkura P, **Mahasandana C**, **Chuansumrit A**, **Angchaisuksiri P**.

Department of Pediatrics, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Several acquired bleeding disorders in the developing world have impacts on health, including late vitamin K deficiency bleeding (VKDB) in infants, dengue haemorrhagic fever (DHF), and malaria. This paper describes their clinical manifestations, mechanisms involved, and treatment.

Publication Types:

- Review

PMID: 15479397 [PubMed - indexed for MEDLINE]

J Thromb Thrombolysis. 2003 Aug-Oct;16(1-2):69-72.

Vitamin K for the treatment of asymptomatic coagulopathy associated with oral anticoagulant therapy.

Crowther MA, **Wilson S**.

Department of Medicine, McMaster University, Hamilton, Ontario, Canada. crowthrm@mcmaster.ca

Patients with asymptomatic elevated International Normalized Ratios (INRs) are commonly seen in practice, but there is no consensus on how best to manage this condition. Evidence suggests that low-dose (1 mg to 2.5 mg) oral vitamin K restores patients to INR values associated with a lower risk of hemorrhage more rapidly than discontinuing warfarin alone. Vitamin K therapy remains under-utilized despite evidence for its effectiveness. The studies discussed in this review suggest that vitamin K1 should be considered if rapid reductions in the INR are desired. For most rapid corrections in the INR, vitamin K should be administered by the intravenous route since it begins to reduce the INR within 8 hours. Subcutaneous vitamin K is relatively ineffective, and its use may be associated with over-correction of the INR.

Publication Types:

- Review

PMID: 14760216 [PubMed - indexed for MEDLINE]

Vitamin K1 and Alzheimer's Disease

J Am Diet Assoc. 2008 Dec;108(12):2095-9.

Low vitamin K intakes in community-dwelling elders at an early stage of Alzheimer's disease.

Presse N, **Shatenstein B**, **Kergoat MJ**, **Ferland G**.

Département de Nutrition, Université de Montréal, Montréal, Canada.

An increasing body of evidence points to a role for vitamin K in brain physiology through its participation in sphingolipid metabolism and biological activation of the vitamin K-dependent protein Gas6. One hypothesis is that vitamin K may also play a role in the pathogenesis of Alzheimer's disease. A recent study found that patients with early-stage Alzheimer's disease consumed less vitamin K than did cognitively intact control subjects. To learn more about the dietary intakes and food sources of vitamin K in these patients, a detailed analysis was conducted. Dietary vitamin K intakes were assessed from 5 nonconsecutive days of food records collected from 31 community-dwelling patients with early-stage Alzheimer's disease and in 31 age- and sex-matched cognitively intact control subjects. Mean vitamin K intake on a person-day basis was 63+/-90 microg/day in patients and 139+/-233 microg/day in control subjects. Vitamin K intakes were significantly less in participants with Alzheimer's disease ($P<0.0001$), even after adjusting for energy intakes ($P=0.0003$). Vegetables, fats, and fruits contributed more than 70% of total vitamin K intake in both groups. The main source of vitamin K was green vegetables, which contributed 33% and 49% to total intakes in patients and control subjects, respectively. This lower consumption of green vegetables in participants with Alzheimer's disease explained their lower vitamin K intakes overall. Despite their limitations, results are in line with the most recent research in both vitamin K and Alzheimer's disease and suggest a need to consider vitamin K in future investigations on the role of diet in Alzheimer's disease.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 19027415 [PubMed - indexed for MEDLINE]

J Am Diet Assoc. 2007 Dec;107(12):2091-9.

Poor nutrient intakes during 1-year follow-up with community-dwelling older adults with early-stage Alzheimer dementia compared to cognitively intact matched controls.

Shatenstein B, **Kergoat MJ**, **Reid I**.

Département de Nutrition, Université de Montréal, Montréal, Canada.
bryna.shatenstein@umontreal.ca

OBJECTIVE: Decreased food intakes, eating behavior disturbances, and loss of body weight are particularly significant problems among those with Alzheimer dementia. To follow the natural evolution of dietary and nutrition status among elderly community-dwelling adults with Alzheimer dementia. METHODS: With their caregivers, 36 community-dwelling patients in early stages of Alzheimer dementia, aged > or =65 years, were recruited from memory clinics in Montréal, age-matched to cognitively intact community-based controls (n=58), and interviewed at four to five time points (T0 to T4) across an 18-month period. Current diet and supplement use were assessed monthly by two food records and/or 24-hour diet recalls (666 records/recalls from patients and 1,678 records/recalls from controls), using adapted data collection techniques among patients, and analyzed using CANDAT with the 2001b Canadian Nutrient File. RESULTS: Nutrient intakes from diet and supplements were higher in control subjects, with significant differences in energy, the macronutrients, calcium, iron, zinc, vitamin K, vitamin A, and dietary fiber as well as n-3 and n-6 fatty acids. Repeated measures analysis of variance confirmed these observations among balanced groups of participants aged > or =70 years with full nutrient data during 12 months' follow-up. CONCLUSIONS: Dietary intakes by persons with Alzheimer dementia are poor compared to cognitively intact age-matched controls. Suboptimal diet is evident early in the onset of the disease. This vulnerable population would benefit from systematic dietary assessment and intervention to prevent further deterioration in food consumption and increased nutritional risk.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18060894 [PubMed - indexed for MEDLINE]

Med Hypotheses. 2001 Aug;57(2):151-5.

The possible role of vitamin K deficiency in the pathogenesis of Alzheimer's disease and in augmenting brain damage associated with cardiovascular disease.

Allison AC.

SurroMed Corporation, Mountain View, California 94043, USA.

The incidence of Alzheimer's disease (AD) increases with age and in carriers of the apolipoprotein E4 genotype. A relative deficiency of vitamin K, affecting the extrahepatic functions of the vitamin, is common in ageing men and women. The concentration of vitamin K is lower in the circulating blood of APOE4 carriers than in that of persons with other APOE genotypes. Evidence is accumulating that vitamin K has important functions in the brain, including the regulation of sulfotransferase activity and the activity of a growth factor/tyrosine kinase receptor (Gas 6/Axl). The hypothesis is now proposed that vitamin K deficiency contributes to the pathogenesis of AD and that vitamin K supplementation may have a beneficial effect in preventing or treating the disease. Vitamin K may also reduce neuronal damage associated with cardiovascular disease.

PMID: 11461163 [PubMed - indexed for MEDLINE]

Vitamin K2 as a Chemopreventative

Vitam Horm. 2008;78:211-26.

Vitamin K2-mediated apoptosis in cancer cells: role of mitochondrial transmembrane potential.

Shibayama-Imazu T, Aiuchi T, Nakaya K.
Laboratory of Biological Chemistry, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawaku, Tokyo 142-8555, Japan.
Vitamin K2 induces differentiation and apoptosis in a wide array of human cancer cell lines. Vitamin K2-mediated apoptosis proceeds much more slowly than the apoptosis induced by conventional anticancer agents. Thus, it is possible to analyze the underlying mechanism in detail. In this chapter, we focus on the pro-apoptotic effects of vitamin K2 on mitochondrial physiology with particular emphasis on changes in mitochondrial membrane potential (DeltaPsim). Upon treatment of ovarian cancer TYK-nu cells with vitamin K2, superoxide is produced after two to three days, followed shortly thereafter by release of mitochondrial cytochrome c. This is accompanied by other apoptotic features such as characteristic morphological changes and DNA fragmentation by day four. Data suggest that superoxide production might cause damage to mitochondrial membranes, open permeability transition pores, and result in disruption of DeltaPsim with subsequent release of cytochrome c. Both vitamin K2-induced production of superoxide and reduction of DeltaPsim are completely inhibited by alpha-tocopherol such that cell viability is retained. Thus, we propose that the loss of DeltaPsim caused by superoxide might be the major cause of apoptosis following exposure to vitamin K2. However, other pathways may be involved since cyclosporin A failed to completely inhibit vitamin K2-induced apoptosis.
PMID: 18374196 [PubMed - indexed for MEDLINE]

J Cancer Res Clin Oncol. 2008 Jul;134(7):803-12. Epub 2008 Jan 17.

Induction of apoptosis in PA-1 ovarian cancer cells by vitamin K2 is associated with an increase in the level of TR3/Nur77 and its accumulation in mitochondria and nuclei.

Sibayama-Imazu T, Fujisawa Y, Masuda Y, Aiuchi T, Nakajo S, Itabe H, Nakaya K.
Laboratory of Biological Chemistry, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo, 142-8555, Japan.
PURPOSE: We examined the growth-inhibitory and apoptosis-inducing effects of vitamin K(2) (VK(2); menaquinone-4) on various lines of human ovarian cancer cells to study the mechanism of induction of apoptosis by VK(2). METHODS: Cell proliferation was determined by XTT method, and apoptotic cells were detected by Hoechst staining. TR3, also known as Nur77 and NGFI-B, was detected by immunoblotting and immunofluorescence analysis. Role of TR3 on induction of apoptosis was examined by a siRNA experiment. RESULTS AND CONCLUSIONS: We found that PA-1 cells were the most sensitive to VK(2) (IC(50) = 5.0 +/- 0.7 microM), while SK-OV-3 cells were resistant to VK(2). Immunoblotting and immunofluorescence analyses indicated that levels of TR3 were elevated in cell lysates 48 h after the start of treatment with 30 microM VK(2). In the VK(2)-treated cells, TR3 accumulated at significant levels in mitochondria, as well as in the nuclei of PA-1 cells. No similar changes were observed in SK-OV-3 cells under the same conditions. Treatment of PA-1 cells with small interfering RNA (siRNA) directed against TR3, and with cycloheximide or SP600125 (an inhibitor of c-jun N-terminal kinase; JNK), separately, inhibited the VK(2)-induced synthesis of TR3 and apoptosis. From these results, we can conclude that an increase in the synthesis of TR3 and the accumulation of TR3 in mitochondria and in nuclei might be involved in the induction of apoptosis by VK(2) and that the synthesis of TR3 might be regulated through a JNK signaling pathway.
PMID: 18202854 [PubMed - indexed for MEDLINE]

Apoptosis. 2006 Sep;11(9):1535-43.

Production of superoxide and dissipation of mitochondrial transmembrane potential by vitamin K2 trigger apoptosis in human ovarian cancer TYK-nu cells.

Shibayama-Imazu T, Sonoda I, Sakairi S, Aiuchi T, Ann WW, Nakajo S, Itabe H, Nakaya K.

Laboratory of Biological Chemistry, School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Tokyo, 142-8555, Japan.

We reported previously that vitamin K(2) selectively induces apoptosis in human ovary cancer cells (TYK-nu cells) and pancreatic cancer cells (MIA PaCa-2 cells) through a mitochondrion-dependent pathway. In the present study, we examined the details of the mechanism of vitamin K(2)-induced apoptosis in TYK-nu cells. We found that superoxide (O(2)(*-)) was produced by TYK-nu cells between 2 and 3 days after the start of treatment with vitamin K(2), whereas it was produced within 30 min after the start of treatment with geranylgeraniol. The vitamin K(2)-induced apoptosis was inhibited by anti-oxidants, such as alpha-tocopherol, Tiron and N-acetyl-L-cysteine (NAC). Furthermore, both the production of superoxide and the induction of apoptosis by vitamin K(2) were inhibited almost completely by cycloheximide, an inhibitor of protein synthesis, suggesting that the synthesis of enzymes for the production of superoxide might be required for these processes. In parallel with the production of superoxide, the mitochondrial transmembrane potential, as measured by staining with Mitotracker Red CMXRos, dissipated during treatment of TYK-nu cells with vitamin K(2) for 3 days. The vitamin K(2)-induced depolarization of mitochondrial membranes was completely inhibited by alpha-tocopherol and, to a lesser extent, by Tiron and NAC. Since alpha-tocopherol reacts with oxygen radicals, such as superoxide, within the hydrophobic environment of the mitochondrial membrane, we postulate that vitamin K(2)-induced oxidative stress in mitochondria might damage mitochondrial membranes, with subsequent release of cytochrome c, the activation of procaspase 3 and, eventually, apoptosis.
PMID: 16763728 [PubMed - indexed for MEDLINE]

Int J Oncol. 2006 Dec;29(6):1501-8.

Apoptosis of liver cancer cells by vitamin K2 and enhancement by MEK inhibition.

Matsumoto K, Okano J, Nagahara T, Murawaki Y.
Second Department of Internal Medicine, Tottori University School of Medicine, Yonago, Tottori 683-8504, Japan.

Vitamin K2 (VK2) is an anti-proliferative agent toward a variety of cancer including hepatocellular carcinoma (HCC). Because the growth inhibitory effect of VK2 to HCC has not been established yet, we investigated it in HCC cells in vitro. VK2 inhibited growth of Hep3B, but not of HepG2, HLF, and Huh6. VK2 induced the cell cycle arrest at the G1 phase and involvement of apoptosis was suggested because the sub-G1 fraction appeared in flow cytometric analysis and nuclear condensation and fragmentation appeared after VK2 treatment. VK2 activated extracellular signal-regulated kinase (ERK)1/2 in a mitogen-activated ERK-regulating kinase (MEK)-dependent manner in Hep3B and Huh6, but not in HepG2 and HLF. When ERK1/2 was inhibited by U0126, apoptosis by VK2 in Hep3B, but not in Huh6, was significantly enhanced. However, Western blot analysis revealed that neither apoptosis induction by VK2 nor enhancement of apoptosis by U0126 was mediated by caspase activation. These data demonstrated that VK2 induced apoptosis and activated the MEK/ERK1/2 signaling pathway in a cell-type specific manner, and a MEK inhibitor could augment the cell death in these cells.
PMID: 17088989 [PubMed - indexed for MEDLINE]

Int J Mol Med. 2006 Feb;17(2):235-43.

Vitamin K2-induced antitumor effects via cell-cycle arrest and apoptosis in gastric cancer cell lines.

Tokita H, Tsuchida A, Miyazawa K, Ohyashiki K, Katayanagi S, Sudo H, Enomoto M, Takagi Y, Aoki T.
Third Department of Surgery and First Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan.

Vitamin K2 (VK2) has a growth inhibitory effect on various types of cancer cells in vitro, and its efficacy has been demonstrated in clinical applications in a number of patients with leukemia and hepatocellular carcinoma. In this study, the effect of cell growth inhibition and apoptosis induction and the concomitant use of an anticancer agent by VK2 (menaquinone: MK4), on gastric cancer cell lines were examined. When 4 kinds of gastric cancer cells (KATO III, MKN7, MKN74 and FU97) were exposed to MK4, the cell growth was inhibited in an MK4 dose-dependent manner. Morphologically, apoptosis induced by MK4 was recognized in FU97, but only a slight number of apoptotic images was recognized in other cell lines. On the contrary, in all the cell lines, the percentage of APO2.7 positive cells increased significantly in the MK4-treated group as compared to the controls. Caspase-3 activity increased significantly in KATO III and FU97 as compared to the controls, while no significant differences were noted in MKN7 or MKN74. Moreover, in all the cell lines, the percentage of G0/G1-phase cells (approximately 70% in KATO III and FU97, and > or =80% in MKN7 and MKN74) increased in comparison to the controls, suggesting that cell-cycle arrest had occurred. All of the gastric cancer cell lines were given MK4 in different concentrations and two kinds of anticancer agent, with the result that cell growth was inhibited by the anticancer agent in a dose-dependent manner when it was given with MK4 in concentrations of up to 10 microM. In conclusion, our results demonstrate that the effect of MK4 on apoptosis and cell-cycle arrest differs in differentiated (MKN7, MKN74) and undifferentiated (KATO III, FU97) gastric cancer cell lines, and that MK4 alone or with anticancer agents has an antitumor effect on gastric cancer cell lines.
PMID: 16391821 [PubMed - indexed for MEDLINE]

Int J Oncol. 2005 Jan;26(1):33-40.

Combination of vitamin K2 plus imatinib mesylate enhances induction of apoptosis in small cell lung cancer cell lines.

Yokoyama T, Miyazawa K, Yoshida T, Ohyashiki K.
First Department of Internal Medicine, Tokyo Medical University, Nishishinjuku, Shinjuku-ku, Tokyo, Japan.

Imatinib mesylate, an inhibitor of tyrosine kinases including BCR-ABL and KIT, inhibits the growth inhibition of small cell lung cancer (SCLC) cell lines in vitro. However, clinical trials of imatinib mesylate alone in patients with SCLC resulted in unsatisfactory outcomes. Vitamin K2 (menaquinone-4: VK2) induces apoptosis and differentiation in leukemia cells. We recently reported that VK2 also induces apoptosis in lung cancer cell lines. In the present study, we focused on the in vitro combined effects of imatinib mesylate plus VK2 on SCLC cell lines such as LU-139, LU-130, NCI-H69 and NCI-H128. Treatment with imatinib mesylate and VK2 for 96 h resulted in suppression of cell growth in a dose-dependent manner in all cell lines tested. The 50% inhibitory concentration (IC50) for imatinib mesylate ranged from 17-29 microM, whereas the IC50 for VK2 ranged from 16-64 microM. Combined treatment of imatinib mesylate plus VK2 resulted in pronounced inhibition of cell growth. The morphologic features of cells treated with imatinib mesylate and VK2 were typical of apoptosis. Since VK2 is a safe medicine without prominent adverse effects, treatment of patients with SCLC could derive therapeutic benefits from a combination of imatinib mesylate and VK2.
PMID: 15586222 [PubMed - indexed for MEDLINE]

Int J Oncol. 2003 Sep;23(3):627-32.

Apoptosis induction of vitamin K2 in lung carcinoma cell lines: the possibility of vitamin K2 therapy for lung cancer.

Yoshida T, Miyazawa K, Kasuga I, Yokoyama T, Minemura K, Ustumi K, Aoshima M, Ohyashiki K.
First Department of Internal Medicine, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.

Vitamin K2 (menaquinone-4: VK2) has been reported to show apoptosis and differentiation-inducing effects on leukemia cells. Furthermore, the clinical benefits of using VK2 have been demonstrated for the treatment of the patients with acute leukemia and myelodysplastic syndromes. In the present study, we examined the in vitro effects of VK2 on lung carcinoma cell lines LU-139 and LU-130 for small cell carcinomas, PC-14 and CCL-185 for adenocarcinomas, LC-AI and LC-1/sq for squamous cell carcinomas, and IA-LM for large cell carcinoma, respectively. Treatment with VK2 for 48 to 96 h resulted in cell growth suppression in a dose-dependent manner in all cell lines tested. IC50 (50% inhibitory concentration) for VK2 ranged from 7.5 to 75 micro M, and there was no relation between the efficacy of growth suppression by VK2 and tissue type of lung carcinoma cell lines. Morphologic features of the cells treated with VK2 were typical for apoptosis along with caspase-3 activation and becoming positive for APO2.7 monoclonal antibody, an antibody which specifically detects the cell undergoing apoptosis. In addition to the leukemia cell line, LU-139 cells accumulated into G0/G1 phase during 72-h exposure to VK2. Combined treatment of cisplatin plus VK2 resulted in enhanced cytocidal effect compared to the cells treated with either cisplatin or VK2 alone. Since VK2 is a safe medicine without prominent adverse effects including bone marrow suppression, our data strongly suggest the therapeutic possibility of using VK2 for the treatment of patients with lung carcinoma.
PMID: 12888897 [PubMed - indexed for MEDLINE]

Int J Mol Med. 2009 Jun;23(6):709-16.

Growth inhibitory effects of vitamin K2 on colon cancer cell lines via different types of cell death including autophagy and apoptosis.

Kawakita H, Tsuchida A, Miyazawa K, Naito M, Shigoka M, Kyo B, Enomoto M, Wada T, Katsumata K, Ohyashiki K, Itoh M, Tomoda A, Aoki T.
Third Department of Surgery, Tokyo Medical University, Tokyo, Japan.

Vitamin K2 (menaquinone-4: MK4) has been reported to inhibit cell growth and induce apoptosis in various tumor cells. We examined the effects of MK4 using three types of colon cancer cell lines: PMCO1, COLO201, and DLD-1. Exposure to MK4 was at concentrations from 5 to 50 microM, growth inhibitory effects were observed dose-dependently in COLO201 and PMCO1, whereas the growth inhibition observed in DLD-1 was minimal. Comparison of COLO201 and PMCO1 cells exhibiting distinct growth inhibitory effects showed that cell death via apoptosis accompanied by activation of caspase-3 was induced in PMCO1, while apoptosis was not induced in COLO201. On the contrary, immunoblot assay using an anti-LC3B antibody showed autophagy induction by addition of MK4 and incubation in all three types of colon cancer cell lines. Addition of 3-methyladenine (3-MA) attenuated the growth inhibitory effect of MK4 in COLO201, whereas no influence of 3-MA was noted in PCMO1. Electron microscopy images of COLO201 showed that addition of MK4 induced an increased number of cytoplasmic autophagosomes and autolysosomes as well as morphological changes including scantiness of cytoplasm accompanied by loss of cell organelles, nuclear shrinkage, and fragmentation of cytoplasmic membrane in some cells, indicating the induction of cell death via autophagy not accompanied by the formation of apoptotic bodies in COLO201 cells. These results suggested that the response to MK4 and the way of induction of cell death vary in different colon cancer cell lines.
PMID: 19424596 [PubMed - indexed for MEDLINE]

Endocr J. 2009;56(7):843-9. Epub 2009 Jun 24.

Vitamin K2 suppresses proliferation and motility of hepatocellular carcinoma cells by activating steroid and xenobiotic receptor.

Azuma K, Urano T, Ouchi Y, Inoue S.

Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

Vitamin K2, known as a cofactor for gamma-carboxylase, also serves as a ligand of a nuclear receptor, Steroid and Xenobiotic Receptor (SXR). Several clinical trials revealed that vitamin K2 reduced de novo formation and recurrence of hepatocellular carcinoma (HCC). To examine the role of SXR in HCC as a receptor activated by vitamin K2, the cells stably overexpressing SXR were established using a HCC cell line, HuH7. Overexpression of SXR resulted in reduced proliferation and motility of the cells. Further suppression of proliferation and motility was observed when SXR overexpressing clones were treated with vitamin K2. These results suggest that the activation of SXR could contribute to tumor suppressive effects of vitamin K2 on HCC cells.

PMID: 19550077 [PubMed - indexed for MEDLINE]

Vitamin K2 as a Chemopreventative

J Gastroenterol. 2009;44(3):228-35. Epub 2009 Feb 13.

Involvement of hepatoma-derived growth factor in the growth inhibition of hepatocellular carcinoma cells by vitamin K(2).

Yamamoto T, Nakamura H, Liu W, Cao K, Yoshikawa S, Enomoto H, Iwata Y, Koh N, Saito M, Imanishi H, Shimomura S, Iijima H, Hada T, Nishiguchi S.

Division of Hepatobiliary and Pancreatic Medicine, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663-8501, Japan.

BACKGROUND: Vitamin K(2) has been reported to suppress the growth of human hepatocellular carcinoma (HCC) in vitro and hepatocarcinogenesis in hepatitis C virus (HCV)-related cirrhosis in vivo. Hepatoma-derived growth factor (HDGF) is a unique nuclear targeting growth factor that is highly expressed in HCC cells and is a possible prognostic factor for patients with HCC. We investigated the regulation of HDGF expression by vitamin K(2). METHODS: Three HCC-derived cell lines, HepG2, HuH-7, and SK-Hep-1, were used. Cell number was determined with the MTT assay. The expression levels of HDGF mRNA and protein were measured by the real-time reverse transcriptase-polymerase chain reaction (PCR) method and ELISA and Western blot analysis, respectively. The HDGF promoter activity was measured by a dual luciferase-reporter assay. RESULTS: Vitamin K(2) suppressed the growth of the three HCC cell lines in a dose-dependent manner. Vitamin K(2) significantly suppressed the expression of the HDGF protein and mRNA in three cell lines. By a luciferase assay, vitamin K(2) significantly suppressed the promoter activity of the HDGF protein. Based on some luciferase-reporter plasmids containing truncated promoter regions, the possible responsive site of vitamin K(2) seems to reside in the region -1 to -150 bp of the HDGF gene. CONCLUSIONS: These findings suggested that regulation of the HDGF gene expression is one of the crucial mechanisms of vitamin K(2)-induced cell growth suppression for HCC.

PMID: 19214667 [PubMed - indexed for MEDLINE]

Cancer Epidemiol Biomarkers Prev. 2009 Jan;18(1):49-56.

Serum undercarboxylated osteocalcin as biomarker of vitamin K intake and risk of prostate cancer: a nested case-control study in the Heidelberg cohort of the European prospective investigation into cancer and nutrition.

Nimptsch K, Rohrmann S, Nieters A, Linseisen J.

Division of Cancer Epidemiology, German Cancer Research Center, Im Neuenheimer Feld 280, Heidelberg DE-69120, Germany.

From cell studies, Vitamin K is known to exert anticancer effects on a variety of cancer cell lines, including prostate cancer cells. Recently, we reported an inverse association between dietary intake of menaquinones (vitamin K(2)), but not phylloquinone (vitamin K(1)), and risk of prostate cancer. In this nested case-control study including 250 prostate cancer cases and 494 matched controls, we aimed to confirm this cancer-protective effect using serum undercarboxylated osteocalcin (ucOC), a biomarker of vitamin K status inversely associated with vitamin K intake. In addition, effect modification by a functionally relevant polymorphism in the vitamin K epoxide reductase gene (VKORC1) was assessed. Serum ucOC and intact total osteocalcin (iOC) were analyzed with the use of ELISA tests. Serum ucOC was expressed relative to iOC (i.e., as ucOC/iOC ratio). Conditional logistic regression was used to calculate multivariate adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Serum ucOC/iOC ratio was positively associated with advanced-stage (OR per 0.1 increment, 1.38; 95% CI, 1.03-1.86) and high-grade prostate cancer (OR, 1.21; 95% CI, 1.00-1.46) but not with total prostate cancer. The significant association with advanced-stage prostate cancer was confirmed when serum ucOC/iOC ratio was jointly modeled with menaquinone intake data. There was indication of a lower prostate cancer risk in carriers of the A allele (compared with GG carriers) of the +2255 VKORC1 polymorphism with increasing menaquinone intake (P(interaction) = 0.14) whereas no distinct effect modification was observed for the ucOC/iOC ratio (P(interaction) = 0.37). The increased risks of advanced-stage and high-grade prostate cancer with higher serum ucOC/iOC ratio strengthen the findings for dietary menaquinone intake.

Vitamin K2 as a Chemopreventative

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The association between dietary vitamin K intake and serum undercarboxylated osteocalcin is modulated by vitamin K epoxide reductase genotype.

Nimptsch K, Nieters A, Hailer S, Wolfram G, Linseisen J.

Unit of Nutritional Epidemiology, Division of Cancer Epidemiology, German Cancer Research Center, Im Neuenheimer Feld 280, Heidelberg DE-69120, Germany.

Vitamin K acts as a cofactor during the gamma-carboxylation of vitamin K-dependent proteins. Undercarboxylated osteocalcin (ucOC) is a suggested biomarker of vitamin K status. The +2255 polymorphism of the vitamin K epoxide reductase gene (VKORC1) was shown to be associated with the recycling rate of the active form of vitamin K. We investigated the association between dietary vitamin K intake and serum ucOC and hypothesized that this association might vary by VKORC1 genotype. ucOC and total intact osteocalcin (iOC) concentrations were quantified using specific ELISA tests in serum samples of 548 male and female participants (aged 18-81 years) of the Bavarian Food Consumption Survey II. ucOC was expressed relative to iOC (ucOC/iOC ratio). Dietary intake of vitamin K (phylloquinone and menaquinones) was estimated from three 24 h dietary recalls using previously published food composition data. The association between dietary vitamin K intake and ucOC/iOC ratio was analysed using linear and non-linear regression models. Median intakes of phylloquinone/menaquinones were 83.4/37.6 microg/d in men and 79.6/29.8 microg/d in women, respectively. As expected, vitamin K intake was significantly inversely associated with the ucOC/iOC ratio. The ucOC/iOC ratio differed significantly across variants of the +2255 polymorphism in the VKORC1 gene. Stratification by VKORC1+2255 genotype revealed that only in carriers of the GG genotype (39 % of all participants) did the ucOC/iOC ratio significantly decrease with increasing intake of vitamin K. Thus, the results show that the inverse association between dietary vitamin K intake and serum ucOC depends on a functionally relevant allelic variant of the VKORC1 gene.

PMID: 19025725 [PubMed - indexed for MEDLINE]

Chemotherapy. 2009;55(1):28-35. Epub 2008 Oct 31.

Vitamin K2 inhibits the growth of hepatocellular carcinoma via decrease of des-gamma-carboxy prothrombin.

Ma M, Qu XJ, Mu GY, Chen MH, Cheng YN, Kokudo N, Tang W, Cui SX.

Department of Pharmacology, School of Pharmaceutical Sciences, Shandong University, Jinan, China.

BACKGROUND: Des-gamma-carboxy prothrombin (DCP) is a serum protein produced by hepatocellular carcinoma (HCC) cells in the absence of vitamin K. Serum and tissue DCP expressions are thought to reflect the biological malignant potential of HCC. Hence, we aimed to examine the efficacy of vitamin K(2) on the production of DCP as well as tumor cell growth and invasion. METHODS: Cell growth and viability were evaluated by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assay. The in vivo efficacy of vitamin K(2) was examined in nude mice bearing HCC cells. A 24-well transwell chamber was used to evaluate the motility and invasive ability of HCC cells. Levels of DCP in supernatant of cultures and in serum of mice were measured using an electrochemiluminescence immunoassay method. Western blot and immunohistochemical analysis were employed to evaluate the expression of DCP in HCC. RESULTS: Vitamin K(2) (2-40 muM) significantly decreased the levels of DCP production in supernatant of PLC/PRF/5 and HepG2 cells and in serum of nude mice bearing HCC xenografts. The inhibition of DCP was also observed using the assays of Western blot analysis in HCC cultures and immunohistochemical analysis in HCC xenografts in mice. As a result of administration of vitamin K(2), the capacity of HCC growth was inhibited and the invasion and migration of tumor cells were decreased. Furthermore, the inhibitory effects of HCC growth were also observed in vivo and the sensitivity was well correlated with the decrease of DCP in the serum of mice. CONCLUSION: Vitamin K(2) might suppress the growth and invasion of HCC cells via decrease of DCP. (c) 2008 S. Karger AG, Basel.

PMID: 18974646 [PubMed - indexed for MEDLINE]

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Combination of vitamin K2 and angiotensin-converting enzyme inhibitor ameliorates cumulative recurrence of hepatocellular carcinoma.

Yoshiji H, Noguchi R, Toyohara M, Ikenaka Y, Kitade M, Kaji K, Yamazaki M, Yamao J, Mitoro A, Sawai M, Yoshida M, Fujimoto M, Tsujimoto T, Kawaratani H, Uemura M, Fukui H.

Third Department of Internal Medicine, Nara Medical University, Shijo-cho 840, Kashihara, Nara 634-8522, Japan. yoshijih@naramed-u.ac.jp

BACKGROUND/AIMS: No chemopreventive agent has been approved against hepatocellular carcinoma (HCC) yet. Since neovascularization plays a pivotal role in HCC, an angiostatic agent is considered as one of the promising approaches. The aim of this study was to elucidate the combined effect of the clinically used vitamin K(2) (VK) and angiotensin-converting enzyme inhibitor (ACE-I) on cumulative recurrence after curative treatment on a total of 87 patients, especially in consideration of neovascularization. METHODS: VK (menatetrenone; 45 mg/day) and/or ACE-I (perindopril; 4 mg/day) were administered for 36-48 months after curative therapy for HCC. The cumulative recurrence and several indices were analyzed. RESULTS: A 48-month follow-up revealed that the combination treatment with VK and ACE-I markedly inhibited the cumulative recurrence of HCC in association with suppression of the serum level of the vascular endothelial growth factor (VEGF); a central angiogenic factor. The serum level of lectin-reactive alpha-fetoprotein was also suppressed almost in parallel with VEGF. These beneficial effects were not observed with single treatment using VK or ACE-I. CONCLUSIONS: The combination treatment of VK and ACE-I may suppress the cumulative recurrence of HCC after the curative therapy, at least partly through suppression of the VEGF-mediated neovascularization.

PMID: 19501932 [PubMed - indexed for MEDLINE]

Dietary intake of vitamin K and risk of prostate cancer in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg).

Nimptsch K, Rohrmann S, Linseisen J.

Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany.

BACKGROUND: Anticarcinogenic activities of vitamin K have been observed in various cancer cell lines, including prostate cancer cells. Epidemiologic studies linking dietary intake of vitamin K with the development of prostate cancer have not yet been conducted. OBJECTIVE: We evaluated the association between dietary intake of phylloquinone (vitamin K1) and menaquinones (vitamin K2) and total and advanced prostate cancer in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition. DESIGN: At baseline, habitual dietary intake was assessed by means of a food-frequency questionnaire. Dietary intake of phylloquinone and menaquinones (MK-4-14) was estimated by using previously published HPLC-based food-content data. Multivariate-adjusted relative risks of total and advanced prostate cancer in relation to intakes of phylloquinone and menaquinones were calculated in 11 319 men by means of Cox proportional hazards regression. RESULTS: During a mean follow-up time of 8.6 y, 268 incident cases of prostate cancer, including 113 advanced cases, were identified. We observed a nonsignificant inverse association between total prostate cancer and total menaquinone intake [multivariate relative risk (highest compared with lowest quartile): 0.65; 95% CI: 0.39, 1.06]. The association was stronger for advanced prostate cancer (0.37; 0.16, 0.88; P for trend = 0.03). Menaquinones from dairy products had a stronger inverse association with advanced prostate cancer than did menaquinones from meat. Phylloquinone intake was unrelated to prostate cancer incidence (1.02; 0.70, 1.48). CONCLUSIONS: Our results suggest an inverse association between the intake of menaquinones, but not that of phylloquinone, and prostate cancer. Further studies of dietary vitamin K and prostate cancer are warranted.

PMID: 18400723 [PubMed - indexed for MEDLINE]

Autophagy. 2008 Jul 1;4(5):629-40. Epub 2008 Mar 20.

Vitamin K2 induces autophagy and apoptosis simultaneously in leukemia cells.

Yokoyama T, Miyazawa K, Naito M, Toyotake J, Tauchi T, Itoh M, Yuo A, Hayashi Y, Georgescu MM, Kondo Y, Kondo S, Ohyashiki K.

First Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan.

Vitamin K2 (menaquinone-4: VK2) is a potent inducer for apoptosis in leukemia cells in vitro. HL-60bcl-2 cells, which are derived from a stable transfectant clone of the human bcl-2 gene into the HL-60 leukemia cell line, show 5-fold greater expression of the Bcl-2 protein compared with HL-60neo cells, a control clone transfected with vector alone. VK2 induces apoptosis in HL-60neo cells, whereas HL-60bcl-2 cells are resistant to apoptosis induction by VK2 but show inhibition of cell growth along with an increase of cytoplasmic vacuoles during exposure to VK2. Electron microscopy revealed formation of autophagosomes and autolysosomes in HL-60bcl-2 cells after exposure to VK2. An increase of acid vesicular organelles (AVOs) detected by acridine orange staining for lysosomes as well as conversion of LC3B-I into LC3B-II by immunoblotting and an increased punctuated pattern of cytoplasmic LC3B by fluorescent immunostaining all supported induction of enhanced autophagy in response to VK2 in HL-60bcl-2 cells. However, during shorter exposure to VK2, the formation of autophagosomes was also prominent in HL-60neo cells although nuclear chromatin condensations and nuclear fragments were also observed at the same time. These findings indicated the mixed morphologic features of apoptosis and autophagy. Inhibition of autophagy by either addition of 3-methyladenine, siRNA for Atg7, or Tet-off Atg5 system all resulted in attenuation of VK2-incuded cell death, indicating autophagy-mediated cell death in response to VK2. These data demonstrate that autophagy and apoptosis can be simultaneously induced by VK2. However, autophagy becomes prominent when the cells are protected from rapid apoptotic death by a high expression level of Bcl-2.

PMID: 18376138 [PubMed - indexed for MEDLINE]

Vitam Horm. 2008;78:211-26.

Vitamin K2-mediated apoptosis in cancer cells: role of mitochondrial transmembrane potential.

Shibayama-Imazu T, Aiuchi T, Nakaya K.

Laboratory of Biological Chemistry, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawaku, Tokyo 142-8555, Japan.

Vitamin K2 induces differentiation and apoptosis in a wide array of human cancer cell lines. Vitamin K2-mediated apoptosis proceeds much more slowly than the apoptosis induced by conventional anticancer agents. Thus, it is possible to analyze the underlying mechanism in detail. In this chapter, we focus on the pro-apoptotic effects of vitamin K2 on mitochondrial physiology with particular emphasis on changes in mitochondrial membrane potential (DeltaPsim). Upon treatment of ovarian cancer TYK-nu cells with vitamin K2, superoxide is produced after two to three days, followed shortly thereafter by release of mitochondrial cytochrome c. This is accompanied by other apoptotic features such as characteristic morphological changes and DNA fragmentation by day four. Data suggest that superoxide production might cause damage to mitochondrial membranes, open permeability transition pores, and result in disruption of DeltaPsim with subsequent release of cytochrome c. Both vitamin K2-induced production of superoxide and reduction of DeltaPsim are completely inhibited by alpha-tocopherol such that cell viability is retained. Thus, we propose that the loss of DeltaPsim caused by superoxide might be the major cause of apoptosis following exposure to vitamin K2. However, other pathways may be involved since cyclosporin A failed to completely inhibit vitamin K2-induced apoptosis.

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Vitam Horm. 2008;78:435-42.

Hepatocellular carcinoma and vitamin K.

Mizuta T, Ozaki I.

Department of Internal Medicine, Saga Medical School, 5-1-1 Nabeshima, Saga, Japan.

On the basis of reports of the antitumor effects of vitamin K on various cancers, we clinically investigated the suppressive effects of vitamin K2 on tumor recurrence after curative treatment for hepatocellular carcinoma (HCC). Our results showed that vitamin K2 administration significantly suppressed HCC recurrence. Our laboratory findings revealed that the inhibitory effect of vitamin K2 against HCC cell growth was generated by suppressing cyclin D1 expression through inhibition of NF-kappaB activation.

PMID: 18374204 [PubMed - indexed for MEDLINE]

Cancer Lett. 2008 May 8;263(1):53-60. Epub 2008 Jan 30.

Vitamin K2 suppresses malignancy of HuH7 hepatoma cells via inhibition of connexin 43.

Kaneda M, Zhang D, Bhattacharjee R, Nakahama K, Arii S, Morita I.

Department of Cellular Physiological Chemistry, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8549, Japan.

The anti-cancer potential of vitamin K(2) (VK(2)) in hepatoma has gained considerable attention but the underlying mechanisms are unclear. Treatment of HuH7 hepatoma cells with VK(2) produced a normal liver phenotype. Following treatment of cells with VK(2), there was an increase in gap junctional intercellular communication activity, accompanied by up-regulation of connexin 32 (Cx32), dominantly expressed in normal hepatocyte. In contrast, Cx43 expression was inhibited. Moreover, the effect of VK(2) on Cx32 was abolished by over-expression of Cx43. Taken together, we propose that the anti-tumor effect of VK(2) is at least partly due to a decrease in Cx43 promoter activity.

PMID: 18249064 [PubMed - indexed for MEDLINE]

J Cancer Res Clin Oncol. 2008 Jul;134(7):803-12. Epub 2008 Jan 17.

Induction of apoptosis in PA-1 ovarian cancer cells by vitamin K2 is associated with an increase in the level of TR3/Nur77 and its accumulation in mitochondria and nuclei.

Sibayama-Imazu T, Fujisawa Y, Masuda Y, Aiuchi T, Nakajo S, Itabe H, Nakaya K.

Laboratory of Biological Chemistry, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawa-ku, Tokyo, 142-8555, Japan.

PURPOSE: We examined the growth-inhibitory and apoptosis-inducing effects of vitamin K(2) (VK(2); menaquinone-4) on various lines of human ovarian cancer cells to study the mechanism of induction of apoptosis by VK(2). METHODS: Cell proliferation was determined by XTT method, and apoptotic cells were detected by Hoechst staining. TR3, also known as Nur77 and NGFI-B, was detected by immunoblotting and immunofluorescence analysis. Role of TR3 on induction of apoptosis was examined by a siRNA experiment. RESULTS AND CONCLUSIONS: We found that PA-1 cells were the most sensitive to VK(2) (IC(50) = 5.0 +/- 0.7 microM), while SK-OV-3 cells were resistant to VK(2). Immunoblotting and immunofluorescence analyses indicated that levels of TR3 were elevated in cell lysates 48 h after the start of treatment with 30 microM VK(2). In the VK(2)-treated cells, TR3 accumulated at significant levels in mitochondria, as well as in the nuclei of PA-1 cells. No similar changes were observed in SK-OV-3 cells under the same conditions. Treatment of PA-1 cells with small interfering RNA (siRNA) directed against TR3, and with cycloheximide or SP600125 (an inhibitor of c-jun N-terminal kinase; JNK), separately, inhibited the VK(2)-induced synthesis of TR3 and apoptosis. From these results, we can conclude that an increase in the synthesis of TR3 and the accumulation of TR3 in mitochondria and in nuclei might be involved in the induction of apoptosis by VK(2) and that the synthesis of TR3 might be regulated through a JNK signaling pathway.

PMID: 18202854 [PubMed - indexed for MEDLINE]

Int J Mol Med. 2007 Dec;20(6):801-8.

Vitamin K2-induced cell growth inhibition via autophagy formation in cholangiocellular carcinoma cell lines.

Enomoto M, Tsuchida A, Miyazawa K, Yokoyama T, Kawakita H, Tokita H, Naito M, Itoh M, Ohyashiki K, Aoki T.

Third Department of Surgery, Tokyo Medical University, Tokyo 160-0023, Japan.

Vitamin K2 (MK4) has antitumor effects on various types of cancer cell lines in vitro, and its efficacy has also been reported in clinical applications for patients with leukemia, myelodysplastic syndrome, and hepatocellular carcinoma (HCC). However, details of the mechanism of the antitumor effects of MK4 remain unclear. In the present study, we examined the antitumor effects of MK4 on cholangiocellular carcinoma (CCC) cell lines and its mechanism of action using the HL-60 leukemia cell line that exerts MK4-induced cell growth inhibition via apoptosis induction and cell cycle arrest as a control. MK4 exerted dose-dependent antitumor effects on all three types of CCC cell lines. However, apoptosis occurred in a smaller percentage of cells and there was less cell cycle arrest compared with other cancer cell lines studied previously, which suggested slight MK4-induced cell growth inhibition via apoptosis induction and cell cycle arrest. On the contrary, histopathological fidings showed a large number of cells containing vacuoles in their cytoplasm, and electron microscopic findings showed a large number of cytoplasmic autophagosomes and autolysosomes. These findings suggested evidence of autophagy-related cell death. Fluorescence microscopy following acridine orange staining revealed an increase in the number of cytoplasmic acidic vesicular organelles characteristic of autophagy. Moreover, there were few cells forming autophagic vesicles in the control group, while the percentage of cells containing vacuoles in the MK4-treated group increased with the duration of culture. These results suggested that, unlike in leukemia, gastric cancer, HCC, and other cancer cells, the antitumor effects of MK4 on CCC cells are induced via autophagy formation.

PMID: 17982686 [PubMed - indexed for MEDLINE]

Hepatol Res. 2007 Sep;37 Suppl 2:S303-7.

Potential role of vitamin K(2) as a chemopreventive agent against hepatocellular carcinoma.

Tamori A, Habu D, Shiomi S, Kubo S, Nishiguchi S.

Department of Hepatology, Osaka City University Graduate School of Medicine, Osaka, Japan.

Vitamin K, a cofactor necessary for the production of several antihemorrhagic factors, can inhibit the growth of various types of cells derived from neoplasms. In hepatoma cells, vitamin K(2) causes cell-cycle arrest and apoptosis. Vitamin K(2) is widely used in Japan to treat osteoporosis. The safety, relatively low cost and ease of use of vitamin K(2) have led to good compliance with treatment. The result of preliminary clinical trials in patients with chronic liver diseases are intriguing and suggest that vitamin K(2) might reduce the risk of hepatocellular carcinoma (HCC) in patients with liver cirrhosis as well as prevent disease recurrence after curative therapy in patients with HCC. This article reviews the potential role of vitamin K(2) as a chemopreventive agent against HCC and discusses future directions for clinical trials.

PMID: 17877500 [PubMed - in process]

World J Gastroenterol. 2007 Jun 21;13(23):3259-61.

Combined treatment of vitamin K2 and angiotensin-converting enzyme inhibitor ameliorates hepatic dysplastic nodule in a patient with liver cirrhosis.

Yoshiji H, Noguchi R, Yamazaki M, Ikenaka Y, Sawai M, Ishikawa M, Kawaratani H, Mashitani T, Kitade M, Kaji K, Uemura M, Yamao J, Fujimoto M, Mitoro A, Toyohara M, Yoshida M, Fukui H.

Third Department of Internal Medicine, Nara Medical University, Shijo-cho 840, Kashihara, Nara 634-8522, Japan. yoshijih@naramed-u.ac.jp

Although it is well known that the hepatocellular carcinoma (HCC) is an ominous complication in patients with liver cirrhosis, there has been no approved drug to prevent the development of HCC to date. We previously reported that the combined treatment of vitamin K2 (VK) and angiotensin-converting enzyme inhibitor (ACE-I) significantly suppressed the experimental hepatocarcinogenesis. A 66-year-old Japanese woman with hepatitis C virus (HCV)-related liver cirrhosis developed a dysplastic nodule in the liver detected by enhanced computed tomography along with elevation of the tumor markers, namely, alpha-fetoprotein (AFP) and lectin-reactive demarcation (AFP-L3), suggesting the presence of latent HCC. After oral administration of VK and ACE-I, the serum levels of both AFP and AFP-L3 gradually decreased without any marked alteration of the serum aminotransferase activity. After one-year treatment, not only the serum levels of AFP and AFP-L3 returned to the normal ranges, but also the dysplastic nodule disappeared. Since both VK and ACE-I are widely used without serious side effects, this combined regimen may become a new strategy for chemoprevention against HCC.

PMID: 17589909 [PubMed - indexed for MEDLINE]

Intern Med. 2007;46(11):711-5. Epub 2007 Jun 1.

Hepatocellular carcinoma with peritoneal dissemination which was regressed during vitamin K2 and vitamin E administration.

Otsuka T, Hagiwara S, Tojima H, Yoshida H, Takahashi T, Nagasaka K, Tomioka S, Ando T, Takeuchi K, Kori T, Ohno Y, Kakizaki S, Takagi H, Mori M.

Department of Internal Medicine, Tone Chuo Hospital, Numata. tcht-otsuka@tonehoken.or.jp

A 65-year-old man with positive anti-hepatitis C antibody and chronic renal failure was diagnosed as having a ruptured hepatocellular carcinoma (HCC) based on computed tomography (CT). The patient underwent transcatheter arterial embolization (TAE) for the HCC. After one more session of TAE, the patient underwent surgery. But HCC seeding peritoneally was pointed out. Vitamin K2 and vitamin E were administered as a conservative treatment. Six months after starting vitamins K2 and E, the primary tumor did not increase in size and intraperitoneal dissemination disappeared on CT with a significant decrease of alpha-fetoprotein. Even though this is only one case, combination therapy of vitamin K2 and E may induce growth suppression of HCC.

PMID: 17541221 [PubMed - indexed for MEDLINE]

J Hepatol. 2007 Jul;47(1):83-92. Epub 2007 Feb 27.

Prevention of hepatocarcinogenesis with phosphatidylcholine and menaquinone-4: in vitro and in vivo experiments.

Sakakima Y, Hayakawa A, Nagasaka T, Nakao A.

Department of Surgery II, Nagoya University School of Medicine, Nagoya, Aichi, Japan.

sakakima@med.nagoya-u.ac.jp

BACKGROUND/AIMS: We examined whether phosphatidylcholine inhibited growth of hepatic cancer, as previously shown for menaquinone-4 (vitamin K2). METHODS: Growth inhibitions by phosphatidylcholine and/or menaquinone-4 and apoptosis induction by phosphatidylcholine were evaluated in vitro using human hepatic cancer cell lines (Hep-3B, Hep-G2, HuH-7, and Alexander). Effects of these agents were then investigated in male Sprague-Dawley rats against hepatocarcinogenesis induced by diethylnitrosamine plus phenobarbital. All rats were killed to examine livers to evaluate inhibitory potential macroscopically and immunohistochemically using an antibody against the marker of carcinogenesis, glutathione S-transferase and apoptotic induction by phosphatidylcholine using TUNEL staining. Blood samples were obtained by cardiac puncture. RESULTS: In vitro, phosphatidylcholine and menaquinone-4 each inhibited cancer cell growth and phosphatidylcholine induced apoptosis dose-dependently. Moreover, exposure to both synergistically inhibited growth in Hep-3B. In vivo, diets containing phosphatidylcholine with or without menaquinone-4 significantly reduced the number of macroscopic hepatic tumor nodules and the extent of abnormally immunoreactive foci conserving hepatic function on serum examinations compared with controls given only the carcinogens. Moreover, phosphatidylcholine supplementation induced apoptosis on TUNEL staining of liver sections. CONCLUSIONS: Given together, phosphatidylcholine and menaquinone-4 may exhibit synergy against hepatocarcinogenesis conserving hepatic function that could benefit patients at high risk for hepatocellular carcinoma.

PMID: 17399847 [PubMed - indexed for MEDLINE]

Haematologica. 2006 May;91(5):613-9.

The mechanisms of vitamin K2-induced apoptosis of myeloma cells.

Tsujioka T, Miura Y, Otsuki T, Nishimura Y, Hyodoh F, Wada H, Sugihara T.

Division of Hematology, Department of Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan.

BACKGROUND AND OBJECTIVES: Physiologically, vitamin K compounds act as co-factors for g-carboxylation of selected glutamates at the N-terminus of prothrombin and some other coagulation factors. These congeners have some growth inhibitory effects of human neoplastic cells. Furthermore, vitamin K2 (VK2) cause apoptosis of some leukemic cells. In search for a new candidate agent to use in the maintenance treatment of myeloma, we analyzed the growth inhibitory effects and apoptosis-inducing capacity of VK2 in human myeloma cells. DESIGN AND METHODS: The growth of myeloma, lymphoma and non-lymphoid cells cultured with various concentrations of VK2 with or without dexamethasone or allopurinol was assayed. Flow cytometry was used to detect apoptotic cells, activated caspase-3 and -9, the generation of superoxide by hydroethidine, and mitochondrial membrane potential (E centym). In addition, the activation of apoptosis-inducing MAPK, p38 and JNK, release of cytochrome c from mitochondria, and change in the relative Bcl-XL/Xs expression balance were analyzed by Western blotting. RESULTS: Myeloma cells and B-cell lymphoma cells were sensitive to VK2. The growth inhibition was caused by apoptosis and activation of caspase-3. The generation of superoxide, and inhibitory effects of the xanthine oxidase inhibitor allopurinol, were demonstrated in myeloma cells. The phosphorylation of MAPK was increased by VK2 in myeloma cells. In addition, the mitochondrial apoptotic pathway was activated. INTERPRETATION AND CONCLUSIONS: VK2 may be a good candidate for myeloma patients, particularly patients who are not suitable candidates for intensive cytoreductive chemotherapy due to age and/or complications.

PMID: 16670066 [PubMed - indexed for MEDLINE]

Vitamin K2 as a Chemopreventative

Vitamins K1 and K2 potentiate hyperthermia by down-regulating Hsp72 expression in vitro and in vivo.

Shimohara S, Murakami T, Morikawa M, Matsuo J, Nagayama S, Shuto T, Suico MA, Okiyoneda T, Yamatsu I, Mizushima T, Shimasaki T, Kai H.

Department of Molecular Medicine, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto 862-0973, Japan.

Hyperthermia is used to treat various malignancies, including esophageal, stomach and rectal cancer. Since hyperthermia alone has produced limited results, much attention has been focused on combining hyperthermia with chemotherapy and on searching for substances able to sensitize tumor cells to hyperthermia-induced damage. Here, we show that vitamins K1 and K2 (VK1, VK2) inhibited the expression of heat-shock protein 72 (Hsp72) but did not affect the constitutive expression of Hsc70 or calnexin in vitro and in vivo. VK1 and VK2 sensitized A549 cells to heat-shock induced cell death, while the compounds alone had no effect on cell viability. The suppression of Hsp72 was apparently at the protein level because the mRNA expression of Hsp72 was unchanged. Moreover, the chaperone activity of Hsp72 was compromised after heat-shock when cells were pre-treated with VK2. The effect of VK2 on Hsp72 suppression, however, was also observed in normal mouse tissue after the mice were subjected to whole-body hyperthermia. To eliminate this side effect, local hyperthermia was performed on tumors in mice. The pre-treatment with VK2 potentiated the effect of local hyperthermia on tumor growth suppression. The findings here that VK1 and VK2 inhibit heat-shock-induced Hsp72 suggest their possible use as an adjuvant for hyperthermia in cancer therapy.

PMID: 16273208 [PubMed - indexed for MEDLINE]

Int J Oncol. 2005 Jan;26(1):33-40.

Combination of vitamin K2 plus imatinib mesylate enhances induction of apoptosis in small cell lung cancer cell lines.

Yokoyama T, Miyazawa K, Yoshida T, Ohyashiki K.

First Department of Internal Medicine, Tokyo Medical University, Nishishinjuku, Shinjuku-ku, Tokyo, Japan.

Imatinib mesylate, an inhibitor of tyrosine kinases including BCR-ABL and KIT, inhibits the growth inhibition of small cell lung cancer (SCLC) cell lines in vitro. However, clinical trials of imatinib mesylate alone in patients with SCLC resulted in unsatisfactory outcomes. Vitamin K2 (menaquinone-4: VK2) induces apoptosis and differentiation in leukemia cells. We recently reported that VK2 also induces apoptosis in lung cancer cell lines. In the present study, we focused on the in vitro combined effects of imatinib mesylate plus VK2 on SCLC cell lines such as LU-139, LU-130, NCI-H69 and NCI-H128. Treatment with imatinib mesylate and VK2 for 96 h resulted in suppression of cell growth in a dose-dependent manner in all cell lines tested. The 50% inhibitory concentration (IC50) for imatinib mesylate ranged from 17-29 microM, whereas the IC50 for VK2 ranged from 16-64 microM. Combined treatment of imatinib mesylate plus VK2 resulted in pronounced inhibition of cell growth. The morphologic features of cells treated with imatinib mesylate and VK2 were typical of apoptosis. Since VK2 is a safe medicine without prominent adverse effects, treatment of patients with SCLC could derive therapeutic benefits from a combination of imatinib mesylate and VK2.

PMID: 15586222 [PubMed - indexed for MEDLINE]

Altern Med Rev. 2003 Aug;8(3):303-18.

The anticancer effects of vitamin K.

Lamson DW, Plaza SM.

Coordinator of Oncology, Bastyr University, Kenmore, Washington, USA. davisl@seanet.com

Vitamin K, an essential nutrient often associated with the clotting cascade, has been the focus of considerable research demonstrating an anticancer potential. Much of this research has focused on vitamin K3, although vitamins K2 and K1 have also been shown to have anticancer effects. Early studies of vitamin K3 employed an oxidative model to explain the anticancer effects seen in both in vitro and in vivo studies; however, this model does not adequately address the action of vitamins K1 and K2. Recent research has demonstrated the anticancer action of vitamin K may act at the level of tyrosine kinases and phosphatases, modulating various transcription factors such as Myc and Fos. Tyrosine kinases associated with cyclins have also been shown to be affected by vitamin K, which can lead to cell cycle arrest and cell death.

PMID: 12946240 [PubMed - indexed for MEDLINE]

J Cancer Res Clin Oncol. 2003 Jan;129(1):1-11. Epub 2002 Dec 17.

Vitamin K(2) selectively induced apoptosis in ovarian TYK-nu and pancreatic MIA PaCa-2 cells out of eight solid tumor cell lines through a mechanism different from geranylgeraniol.

Shibayama-Imazu T, Sakairi S, Watanabe A, Aiuchi T, Nakajo S, Nakaya K.

Laboratory of Biological Chemistry, School of Pharmaceutical Sciences, Showa University, Hatanodai, Shinagawaku, Tokyo 142-8555, Japan. imazuto@pharm.showa-u.ac.jp

PURPOSE: In this study, we examined the effects of vitamin K(2) (menaquinone 4), which has a geranylgeranyl side chain, on various lines of cells derived from human solid tumors and compared them with the effects of geranylgeraniol (GGO). METHODS: Cell proliferation was determined with 3'-[1-[(phenylamino)carbonyl]-3,4-tetrazolium- bis (4-methoxy-6-nitro) benzene-sulfonic acid hydrate (XTT), and the induction of apoptosis was analyzed by TUNEL staining and flow cytometry as well as by measurement of DNA fragmentation, released nucleosomes and caspase-3 activity. Levels of Bcl-2, Bax and cytochrome c were determined by immunoblotting. RESULTS: GGO inhibited the growth of all eight cell lines derived from solid tumors, while vitamin K(2) selectively inhibited the proliferation of ovarian TYK-nu and pancreatic MIA PaCa-2 cancer cells, inducing apoptosis in both cell lines. Far more time was required for the induction of apoptosis in these two cell lines by vitamin K(2) than by GGO. Apoptotic signals induced in TYK-nu cells during the first 2 days that followed the addition of vitamin K(2) to the culture medium were reversible, but these signals became irreversible after 3 days of treatment with vitamin K(2). The induction of apoptosis in TYK-nu cells by vitamin K(2) was inhibited by cycloheximide and also by starvation at a low concentration of serum. Neither cycloheximide nor starvation had any effect on the induction of apoptosis by GGO. Cytochrome c was released simultaneously with the initiation of apoptosis on treatment of TYK-nu cells with vitamin K(2) or GGO. However, GGO induced the release of cytochrome c from isolated mitochondria, while vitamin K(2) did not. The amount of Bcl-2 in TYK-nu cells was reduced by vitamin K(2), but not by GGO. CONCLUSIONS: In contrast to GGO, vitamin K(2) induced apoptosis selectively in pancreatic MIA-PaCa 2 and ovarian TYK-nu cancer cells. It is suggested that de novo protein synthesis might be necessary for induction of apoptosis by vitamin K(2) but not by GGO, and thus, that vitamin K(2) and GGO might induce apoptosis by different mechanisms.

Vitamin K2 as a Chemopreventative

J Neurooncol. 2000 Mar;47(1):31-8.

Cytotoxic effect through fas/APO-1 expression due to vitamin K in human glioma cells.

Sun LK, Yoshii Y, Miyagi K.

Department of Neurosurgery, University of the Ryukyus, Faculty of Medicine, Okinawa, Japan.

Congeners of vitamin K have been found to inhibit growth in various rodent and human tumor cells, but the mechanisms of the inhibitory action are still not well understood. To investigate the modes of actions of vitamin K, we used several vitamin K analogs and examined their cytotoxic effect for human glioma cell lines RBR17T and U251. The analogs included vitamin K1 (VK1), vitamin K2 (VK2), vitamin K3 (VK3), and geranylgeraniol (GGO) which form an unsaturated side chain of VK2. Cell viability was estimated by MTT assay. DNA fragmentation was demonstrated by gel electrophoresis and flow cytometry. In order to study the mechanism of apoptosis, we measured the changes of intracellular reactive oxygen intermediates (ROI) and Fas/APO-1 expression by flow cytometry. The results showed: (1) VK2, VK3, and GGO inhibited cell growth; (2) VK3 had a more potent cytotoxic effect than VK2, and VK3 enhanced the cytotoxic effect of antitumor agents (ACNU and IFN-beta) in RBR17T cells; (3) VK2, VK3, and GGO induce apoptosis: (4) VK3 increased the expression of Fas/APO-1 although VK2 and GGO did not increase its expression in glioma cells; (5) VK3 increased the production of intracellular ROI. Catalase and reduced glutathione (GSH) inhibited production of intracellular ROI and antagonized inhibition of cell-growth induced by VK3, but failed to antagonize that of VK2 and GGO. We hypothesize that VK3 induces apoptosis by promoting the generation of intracellular ROI and Fas/APO-1 expression. On the other hand, VK2 and GGO induce apoptosis but most likely by some other unknown pathway.

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Jpn J Cancer Res. 2000 Jan;91(1):68-74.

Vitamin K contents in liver tissue of hepatocellular carcinoma patients.

Miyakawa T, Kajiwara Y, Shirahata A, Okamoto K, Itoh H, Ohsato K.

Department of Pediatrics, School of Medicine, University of Occupational and Environmental Health, Japan.
t-miya@med.uoeh-u.ac.jp

Serum protein induced in vitamin K absence-II (PIVKA-II) is used as a tumor marker because it increases at a notably higher rate in patients with hepatocellular carcinoma. To clarify the mechanism causing the elevation of serum PIVKA-II, we measured the contents of vitamins K1 (phylloquinone, PK) and K2 (menaquinone, MK) (MK-4, MK-5, MK-6, MK-7, MK-8, MK-9, MK-10) in liver tissue resected from 21 hepatic cancer patients (12 patients with hepatocellular carcinoma and 9 patients with metastatic hepatic cancer), using HPLC combined with coulometric reduction and fluorometric detection. In the cancerous tissue of hepatocellular carcinoma patients, PK, MK-7, MK-8, and MK-10 were significantly lower than that found in the noncancerous tissue. Furthermore, MK-6, MK-7, MK-8, and MK-10 in the cancerous tissue of hepatocellular carcinoma patients were significantly lower than that in the cancerous tissue of metastatic hepatic cancer patients. These data suggested that one of the mechanisms of the elevation of serum PIVKA-II levels in hepatocellular carcinoma patients is a vitamin K deficiency in the local cancerous tissue.

PMID: 10744046 [PubMed - indexed for MEDLINE]

Leukemia. 1997 Jun;11(6):779-87.

Vitamin K2 and its derivatives induce apoptosis in leukemia cells and enhance the effect of all-trans retinoic acid.

Yaguchi M, Miyazawa K, Katagiri T, Nishimaki J, Kizaki M, Tohyama K, Toyama K.

1st Department of Internal Medicine (Hematology/Oncology), Tokyo Medical College, Shinjuki-ku, Japan.

Geranylgeraniol, a polyprenylalcohol composing the side chain of vitamin K2 (VK2), was previously reported to be a potent inducer of apoptosis in tumor cell lines (Ohzumi H et al, J Biochem 1995; 117: 11-13). We examined the apoptosis-inducing ability of VK2 (menaquinone 3 (MK3), MK4 and MK5) and its derivatives such as phytonadione (VK1), as well as polyprenylalcohols with side chains of various lengths including farnesol (C15-OH; FO), geranylgeraniol (C20-OH; GGO), and geranylfarnesol (C25-OH; GFO) toward leukemia cells in vitro. MK3, MK4, MK5 and GFO (at 10 microM) showed a potent apoptosis-inducing activity for all freshly isolated leukemia cells tested and for leukemia cell lines such as NB4, an acute promyelocytic leukemia (APL)-derived cell line and MDS92, a cell line derived from a patient with myelodysplastic syndrome, although there were some differences depending on the cells tested. In contrast, VK1 showed no effect on any of the leukemia cells. The combination of MK5 plus all-trans retinoic acid (ATRA) resulted in enhanced induction of apoptosis in both freshly isolated APL cells and NB4 cells as compared to each reagent alone. These data suggest the possibility of using VK2 and its derivatives for the treatment of myelogenous leukemias, including APL.

PMID: 9177427 [PubMed - indexed for MEDLINE]

Cancer. 1992 Jan 1;69(1):31-8.

Changes of plasma des-gamma-carboxy prothrombin levels in patients with hepatocellular carcinoma in response to vitamin K.

Furukawa M, Nakanishi T, Okuda H, Ishida S, Obata H.

Institute of Gastroenterology, Tokyo Women's Medical College, Japan.

The effect of menaquinone-4 (MK-4, vitamin K2) was studied on des-gamma-carboxy prothrombin (DCP or PIVKA-II) levels in three subjects with vitamin K deficiency and five patients with hepatocellular carcinoma (HCC) with positive DCP. The half-life of DCP in HCC patients after intravenous MK-4 administration (50 mg daily for 14 days) was determined to be 60 hours, identical to that found in vitamin K-deficient subjects who received MK-4. When a single dose of MK-4 (10 mg) was given intravenously to three patients with HCC and elevated DCP, the levels decreased with a reduction rate identical to that in vitamin K-deficient subjects for the first 1 to 3 days, followed by an increase reaching the previous level in 7 to 10 days. Changes in plasma coagulant activity were compared between subjects with vitamin K deficiency and those with HCC before and after a single dose of MK-4 (10 mg). The activity increased in DCP-positive patients with HCC as in vitamin K-deficient subjects who received the same single dose of MK-4. The increase was greater in HCC patients with higher DCP levels. These results suggest that the level of plasma DCP in patients with HCC responded to vitamin K with the same sensitivity as that in vitamin K-deficient subjects. When patients with HCC underwent effective tumor therapy (resection or arterial embolization), the reduction rate (slope of DCP decline) was found to be identical to that in vitamin K-deficient subjects given with MK-4. In patients with less effective therapy, the reduction rate was smaller, or there was an increase in DCP. These observations strongly suggest that sequential measurements of the DCP reduction rate after treatment for HCC are useful for assessing therapeutic effects.

PMID: 1309308 [PubMed - indexed for MEDLINE]

Vitamin K2 as a Hepatoprotective

Chemotherapy. 2009;55(1):28-35. Epub 2008 Oct 31.

Vitamin K2 inhibits the growth of hepatocellular carcinoma via decrease of des-gamma-carboxy prothrombin.

Ma M, Qu XJ, Mu GY, Chen MH, Cheng YN, Kokudo N, Tang W, Cui SX.
Department of Pharmacology, School of Pharmaceutical Sciences, Shandong University, Jinan, China.

BACKGROUND: Des-gamma-carboxy prothrombin (DCP) is a serum protein produced by hepatocellular carcinoma (HCC) cells in the absence of vitamin K. Serum and tissue DCP expressions are thought to reflect the biological malignant potential of HCC. Hence, we aimed to examine the efficacy of vitamin K(2) on the production of DCP as well as tumor cell growth and invasion. METHODS: Cell growth and viability were evaluated by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assay. The in vivo efficacy of vitamin K(2) was examined in nude mice bearing HCC cells. A 24-well transwell chamber was used to evaluate the motility and invasive ability of HCC cells. Levels of DCP in supernatant of cultures and in serum of mice were measured using an electrochemiluminescence immunoassay method. Western blot and immunohistochemical analysis were employed to evaluate the expression of DCP in HCC. RESULTS: Vitamin K(2) (2-40 muM) significantly decreased the levels of DCP production in supernatant of PLC/PRF/5 and HepG2 cells and in serum of nude mice bearing HCC xenografts. The inhibition of DCP was also observed using the assays of Western blot analysis in HCC cultures and immunohistochemical analysis in HCC xenografts in mice. As a result of administration of vitamin K(2), the capacity of HCC growth was inhibited and the invasion and migration of tumor cells were decreased. Furthermore, the inhibitory effects of HCC growth were also observed in vivo and the sensitivity was well correlated with the decrease of DCP in the serum of mice. CONCLUSION: Vitamin K(2) might suppress the growth and invasion of HCC cells via decrease of DCP. (c) 2008 S. Karger AG, Basel.
PMID: 18974646 [PubMed - indexed for MEDLINE]

Am J Gastroenterol. 2002 Apr;97(4):978-81.

Vitamin K2 (menatetrenone) for bone loss in patients with cirrhosis of the liver.

Shiomi S, Nishiguchi S, Kubo S, Tamori A, Habu D, Takeda T, Ochi H.

Third Department of Internal Medicine, Osaka City University Medical School, Osaka, Japan.

Comment in:

- Am J Gastroenterol. 2002 Apr;97(4):786-8.

OBJECTIVE: Bone loss frequently appears in the natural history of liver disease. The effects of therapy for osteoporosis associated with cirrhosis of the liver are still controversial. We evaluated the effects of vitamin K2 on osteopenia in women with cirrhosis. METHODS: The subjects were 50 women with cirrhosis who had underlying hepatitis viral infections. Half of the patients were randomly assigned to receive vitamin K2 (menatetrenone). The bone mineral density (BMD) of the lumbar vertebrae was measured by dual-energy X-ray absorptiometry at entry and at 1-yr intervals for 2 yr. RESULTS: The percentages of change from the initial BMD at 1 and 2 yr after initiation of the study were, respectively, +0.1 +/- 2.6% and -0.5 +/- 3.5% for the vitamin K2-treated group and -2.2 +/- 2.4% and -4.6 +/- 3.9% for the control group. The changes in BMD at each timepoint differed significantly between the control and treated groups ($p = 0.008$ for 1 yr and $p = 0.002$ for 2 yr). In the vitamin K2-treated group, the ratio of osteocalcin to undercarboxylated osteocalcin in those patients with increases in BMD after 1 yr of treatment was significantly lower than that in patients showing decreases in BMD ($p = 0.017$). No adverse effects of vitamin K2 were noted. CONCLUSIONS: Vitamin K2 can prevent bone loss and may therefore be useful in the management of bone disease in women with cirrhosis of the liver.

PMID: 12003435 [PubMed - indexed for MEDLINE]

Vitamin K2 as a Hepatoprotective

Thromb Haemost. 2008 Oct;100(4):530-47.

Metabolism and cell biology of vitamin K.

Shearer MJ, Newman P.

Centre for Haemostasis and Thrombosis, St Thomas' Hospital, Westminster Bridge Road, London, UK.
martin.shearer@gstt.nhs.uk

Naturally occurring vitamin K compounds comprise a plant form, phylloquinone (vitamin K(1)) and a series of bacterial menaquinones (MKs) (vitamin K(2)). Structural differences in the isoprenoid side chain govern many facets of metabolism of K vitamins including the way they are transported, taken up by target tissues, and subsequently excreted. In the post-prandial state, phylloquinone is transported mainly by triglyceride-rich lipoproteins (TRL) and long-chain MKs mainly by low-density lipoproteins (LDL). TRL-borne phylloquinone uptake by osteoblasts is an apoE-mediated process with the LRP1 receptor playing a predominant role. One K(2) form, MK-4, has a highly specific tissue distribution suggestive of local synthesis from phylloquinone in which menadione is an intermediate. Both phylloquinone and MKs activate the steroid and xenobiotic receptor (SXR) that initiates their catabolism, but MK-4 specifically upregulates two genes suggesting a novel MK-4 signalling pathway. Many studies have shown specific clinical benefits of MK-4 at pharmacological doses for osteoporosis and cancer although the mechanism(s) are poorly understood. Other putative non-cofactor functions of vitamin K include the suppression of inflammation, prevention of brain oxidative damage and a role in sphingolipid synthesis. Anticoagulant drugs block vitamin K recycling and thereby the availability of reduced vitamin K. Under extreme blockade, vitamin K can bypass the inhibition of Gla synthesis in the liver but not in the bone and the vessel wall. In humans, MK-7 has a greater efficacy than phylloquinone in carboxylating both liver and bone Gla proteins. A daily supplement of phylloquinone has shown potential for improving anticoagulation control.

PMID: 18841274 [PubMed - indexed for MEDLINE]

World J Gastroenterol. 2007 Jun 21;13(23):3259-61.

Combined treatment of vitamin K2 and angiotensin-converting enzyme inhibitor ameliorates hepatic dysplastic nodule in a patient with liver cirrhosis.

Yoshiji H, Noguchi R, Yamazaki M, Ikenaka Y, Sawai M, Ishikawa M, Kawaratani H, Mashitani T, Kitade M, Kaji K, Uemura M, Yamao J, Fujimoto M, Mitoro A, Toyohara M, Yoshida M, Fukui H.

Third Department of Internal Medicine, Nara Medical University, Shijo-cho 840, Kashihara, Nara 634-8522, Japan. yoshijih@naramed-u.ac.jp

Although it is well known that the hepatocellular carcinoma (HCC) is an ominous complication in patients with liver cirrhosis, there has been no approved drug to prevent the development of HCC to date. We previously reported that the combined treatment of vitamin K2 (VK) and angiotensin-converting enzyme inhibitor (ACE-I) significantly suppressed the experimental hepatocarcinogenesis. A 66-year-old Japanese woman with hepatitis C virus (HCV)-related liver cirrhosis developed a dysplastic nodule in the liver detected by enhanced computed tomography along with elevation of the tumor markers, namely, alpha-fetoprotein (AFP) and lectin-reactive demarcation (AFP-L3), suggesting the presence of latent HCC. After oral administration of VK and ACE-I, the serum levels of both AFP and AFP-L3 gradually decreased without any marked alteration of the serum aminotransferase activity. After one-year treatment, not only the serum levels of AFP and AFP-L3 returned to the normal ranges, but also the dysplastic nodule disappeared. Since both VK and ACE-I are widely used without serious side effects, this combined regimen may become a new strategy for chemoprevention against HCC.

PMID: 17589909 [PubMed - indexed for MEDLINE]

Hepatogastroenterology. 2007 Oct-Nov;54(79):2073-7.

Effect of vitamin K2 on the recurrence in patients with hepatocellular carcinoma.

Hotta N, Ayada M, Sato K, Ishikawa T, Okumura A, Matsumoto E, Ohashi T, Kakumu S.
Department of Internal Medicine, Division of Gastroenterology, Aichi Medical University School of Medicine, Aichi, Japan. naokiki@aol.com

BACKGROUND/AIMS: Vitamin K2 (VK2) appears to have a potent inhibitory activity for cell growth including HCC cells. We investigated whether VK2 could reduce incidence of tumor recurrence after treatment of HCC. Forty-five patients with cured or possibly cured HCC were randomly selected, assigning patients to treatment (n=21) or control group (n=24) with randomization list. METHODOLOGY: For the treatment group, forty-five mg of Glakay was given orally every day after therapy for HCC. No patients complained of adverse effects. Abdominal ultrasonography and dynamic CT were performed at 3-month intervals. Recurrence was confirmed by abdominal angiography. RESULTS: Recurrence of HCC occurred in 7 cases (33.3%) for the treatment group and 12 cases (50.0%) for the control group during mean observation periods of 19.5 and 16.5 months, respectively. Administration of VK2 was not an independent variable for the recurrence on univariate analysis. Cumulative incidence of HCC recurrence did not differ between the two groups, and the cumulative survival rate tended to be high in treatment group (p =0.054). Cox regression analysis revealed that serum albumin concentration alone was an independent factor affecting the recurrence. CONCLUSIONS: These findings suggest that VK2 does not appear to prevent recurrence of HCC after curative treatment. Our study is preliminary and large-scale trials are needed to determine whether VK2 is of benefit to decrease the recurrence of HCC.
PMID: 18251162 [PubMed - indexed for MEDLINE]

Clin Cancer Res. 2007 Apr 1;13(7):2236-45.

Menatetrenone, a vitamin K2 analogue, inhibits hepatocellular carcinoma cell growth by suppressing cyclin D1 expression through inhibition of nuclear factor kappaB activation.

Ozaki I, Zhang H, Mizuta T, Ide Y, Eguchi Y, Yasutake T, Sakamaki T, Pestell RG, Yamamoto K.
Division of Hepatology and Metabolism, Department of Internal Medicine, and Health Administration Center, Saga Medical School, Saga University, Nabeshima, Saga, Japan.
ozaki@cc.saga-u.ac.jp

PURPOSE: Menatetrenone, a vitamin K2 analogue, plays an important role in the production of blood coagulation factors. Menatetrenone has also bee shown to have antineoplastic effects against several cancer cell lines including hepatocellular carcinoma (HCC) cells. However, the mechanisms by which vitamin K2 inhibits HCC cell growth have not bee fully clarified, and we therefore investigated the molecular basis of vitamin K2-induced growth inhibition of HCC cells. EXPERIMENTAL DESIGN: HCC cells were treated with vitamin K2 and the expression of several growth-related genes including cyclin-dependent kinase inhibitors and cyclin D1 was examined at the mRNA and protein levels. A reporter gene assay of the cyclin D1 promoter was done under vitamin K2 treatment. The regulation of nuclear factor kappaB (NF-kappaB) activation was investigated by a NF-kappaB reporter gene assay, an electrophoretic mobility shift assay, a Western blot for phosphorylated IkappaB, and an in vitro kinase assay for IkappaB kinase (IKK). We also examined the effect of vitamin K2 on the growth of HCC cells transfected with p65 or cyclin D1. RESULTS: Vitamin K2 inhibited cyclin D1 mRNA and protein expression in a dose-dependent manner in the HCC cells. Vitamin K2 also suppressed the NF-kappaB binding site-dependent cyclin D1 promoter activity and suppressed the basal, 12-O-tetradecanoylphorbol-13-acetate (TPA)-, TNF-alpha-, and interleukin (IL)-1-induced activation of NF-kappaB binding and transactivation. Concomitant with the suppression of NF-kappaB activation, vitamin K2 also inhibited the phosphorylation and degradation of IkappaBalpha and suppressed IKK kinase activity. Moreover, HCC cells overexpressing cyclin D1 and p65 became resistant to vitamin K2 treatment. CONCLUSION: Vitamin K2 inhibits the growth of HCC cells via suppression of cyclin D1 expression through the IKK/IkappaB/NF-kappaB pathway and might therefore be useful for treatment of HCC.
PMID: 17404108 [PubMed - indexed for MEDLINE]

Intern Med. 2007;46(11):711-5. Epub 2007 Jun 1.

Hepatocellular carcinoma with peritoneal dissemination which was regressed during vitamin K2 and vitamin E administration.

Otsuka T, Hagiwara S, Tojima H, Yoshida H, Takahashi T, Nagasaka K, Tomioka S, Ando T, Takeuchi K, Kori T, Ohno Y, Kakizaki S, Takagi H, Mori M.
Department of Internal Medicine, Tone Chuo Hospital, Numata. tcht-otsuka@tonehoken.or.jp

A 65-year-old man with positive anti-hepatitis C antibody and chronic renal failure was diagnosed as having a ruptured hepatocellular carcinoma (HCC) based on computed tomography (CT). The patient underwent transcatheter arterial embolization (TAE) for the HCC. After one more session of TAE, the patient underwent surgery. But HCC seeding peritoneally was pointed out. Vitamin K2 and vitamin E were administered as a conservative treatment. Six months after starting vitamins K2 and E, the primary tumor did not increase in size and intraperitoneal dissemination disappeared on CT with a significant decrease of alpha-fetoprotein. Even though this is only one case, combination therapy of vitamin K2 and E may induce growth suppression of HCC.
PMID: 17541221 [PubMed - indexed for MEDLINE]

Cancer Sci. 2007 Mar;98(3):431-7.

Synergistic growth inhibition by acyclic retinoid and vitamin K2 in human hepatocellular carcinoma cells.

Kanamori T, Shimizu M, Okuno M, Matsushima-Nishiwaki R, Tsurumi H, Kojima S, Moriwaki H.
Department of Medicine, Gifu University School of Medicine, Gifu, Japan.

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide. However, effective chemopreventive and chemotherapeutic agents for this cancer have not yet been developed. In clinical trials acyclic retinoid (ACR) and vitamin K(2) (VK(2)) decreased the recurrence rate of HCC. In the present study we examined the possible combined effects of ACR or another retinoid 9-cis retinoic acid (9cRA) plus VK(2) in the HuH7 human HCC cell line. We found that the combination of 1.0 microM ACR or 1.0 microM 9cRA plus 10 microM VK(2) synergistically inhibited the growth of HuH7 cells without affecting the growth of Hc normal human hepatocytes. The combined treatment with ACR plus VK(2) also acted synergistically to induce apoptosis in HuH7 cells. Treatment with VK(2) alone inhibited phosphorylation of the retinoid X receptor (RXR)alpha protein, which is regarded as a critical factor for liver carcinogenesis, through inhibition of Ras activation and extracellular signal-regulated kinase phosphorylation. Moreover, the inhibition of RXRalpha phosphorylation by VK(2) was enhanced when the cells were cotreated with ACR. The combination of retinoids plus VK(2) markedly increased both the retinoic acid receptor responsive element and retinoid X receptor responsive element promoter activities in HuH7 cells. Our results suggest that retinoids (especially ACR) and VK(2) cooperatively inhibit activation of the Ras/MAPK signaling pathway, subsequently inhibiting the phosphorylation of RXRalpha and the growth of HCC cells. This combination might therefore be effective for the chemoprevention and chemotherapy of HCC.
PMID: 17270033 [PubMed - indexed for MEDLINE]

Cancer. 2006 Feb 15;106(4):867-72.

JAMA. 2004 Jul 21;292(3):358-61.

Role of vitamin K2 in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver.

Habu D, Shiomi S, Tamori A, Takeda T, Tanaka T, Kubo S, Nishiguchi S.
Department of Hepatology, Graduate School of Medicine, Osaka City University, Osaka, Japan.
Comment in:
JAMA. 2004 Dec 1;292(21):2580-1; author reply 2581.

CONTEXT: Previous findings indicate that vitamin K2 (menaquinone) may play a role in controlling cell growth. OBJECTIVE: To determine whether vitamin K2 has preventive effects on the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. DESIGN, SETTING, AND PARTICIPANTS: Forty women diagnosed as having viral liver cirrhosis were admitted to a university hospital between 1996 and 1998 and were randomly assigned to the treatment or control group. The original goal of the trial was to assess the long-term effects of vitamin K2 on bone loss in women with viral liver cirrhosis. However, study participants also satisfied criteria required for examination of the effects of such treatment on the development of hepatocellular carcinoma. INTERVENTIONS: The treatment group received 45 mg/d of vitamin K2 (n = 21). Participants in the treatment and control groups received symptomatic therapy to treat ascites, if necessary, and dietary advice. MAIN OUTCOME MEASURE: Cumulative proportion of patients with hepatocellular carcinoma. RESULTS: Hepatocellular carcinoma was detected in 2 of the 21 women given vitamin K2 and 9 of the 19 women in the control group. The cumulative proportion of patients with hepatocellular carcinoma was smaller in the treatment group (log-rank test, P =.02). On univariate analysis, the risk ratio for the development of hepatocellular carcinoma in the treatment group compared with the control group was 0.20 (95% confidence interval [CI], 0.04-0.91; P =.04). On multivariate analysis with adjustment for age, alanine aminotransferase activity, serum albumin, total bilirubin, platelet count, alpha-fetoprotein, and history of treatment with interferon alfa, the risk ratio for the development of hepatocellular carcinoma in patients given vitamin K2 was 0.13 (95% CI, 0.02-0.99; P =.05). CONCLUSION: There is a possible role for vitamin K2 in the prevention of hepatocellular carcinoma in women with viral cirrhosis.
PMID: 15265851 [PubMed - indexed for MEDLINE]

Hepatology. 2004 Jul;40(1):243-51.

Vitamin K2 inhibits the growth and invasiveness of hepatocellular carcinoma cells via protein kinase A activation.

Otsuka M, Kato N, Shao RX, Hoshida Y, Ijichi H, Koike Y, Taniguchi H, Moriyama M, Shiratori Y, Kawabe T, Omata M.
Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

Hepatocellular carcinoma (HCC) is a common human malignancy. Its high mortality rate is mainly a result of high intrahepatic recurrence and portal venous invasion (PVI). We previously reported that the development of PVI is related to levels of des-gamma-carboxy prothrombin (DCP), a serum protein that increases at a notably higher rate in patients with HCC. Because DCP is produced by a vitamin K shortage, we examined the biological effects of extrinsic supplementation of vitamin K(2) in HCC cells in vitro and in vivo. Consequently, vitamin K(2) inhibits the growth and invasion of HCC cells through the activation of protein kinase A, which modulates the activities of several transcriptional factors and inhibits the small GTPase Rho, independent of suppression of DCP. In addition, administration of vitamin K(2) to nude mice inoculated with liver tumor cells reduced both tumor growth and body weight loss. In conclusion, similar to an acyclic retinoid--which was previously reported to prevent the recurrence of HCC--vitamin K(2), another lipid-soluble vitamin, may be a promising therapeutic means for the management of HCC.
PMID: 15239108 [PubMed - indexed for MEDLINE]

Hepatol Res. 2009 Nov;39(11):1108-17. Epub 2009 Jul 13.

Vitamin K2 downregulates the expression of fibroblast growth factor receptor 3 in human hepatocellular carcinoma cells.

Cao K, Liu W, Nakamura H, Enomoto H, Yamamoto T, Saito M, Imanishi H, Shimomura S, Cao P, Nishiguchi S.
Division of Hepatobiliary and Pancreatic Medicine, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.

Aim: Vitamin K2 exerts an antitumor activity on human hepatocellular carcinoma (HCC), however, its inhibitory mechanism has not yet been clarified. This study was designed to identify the attractive target molecule of vitamin K2 and shed some light on its effects on fibroblast growth factor receptor (FGFR)3 in HCC cells. Methods: The changes in the gene expression of HuH-7 after vitamin K2 treatment were evaluated by a DNA chip analysis. The mRNA and protein levels of FGFR were evaluated by semiquantitative reverse transcription polymerase chain reaction (RT-PCR), real-time PCR and western blot analysis. The promoter activity of the FGFR3 gene was measured by a dual-luciferase assay. Results: The DNA chip analysis revealed different inhibitory rates of gene expression of FGFR3 (60.6%) and FGFR1 (19.4%) after vitamin K2 treatment. Vitamin K2 suppresses the proliferation of HuH-7 in a dose-dependent manner and its inhibitory rate reached approximately 61.8% at the dose of 30 microM. FGFR3 mRNA was significantly reduced based on semiquantitative RT-PCR and decreased 61.5% by a real-time PCR method after vitamin K2 treatment, but FGFR1 mRNA was not. The level of FGFR3 protein was also reduced by vitamin K2 treatment. The luciferase assay demonstrated that vitamin K2 significantly suppressed the promoter activity of FGFR3. Furthermore, the FGFR3-ERK1/2 signaling pathway was suppressed by vitamin K2 treatment. Conclusion: These findings suggest that vitamin K2 may suppress the proliferation of HCC cells through the downregulation of the FGFR3 expression. The transcriptional suppression of FGFR3 may be a novel mechanism of the vitamin K2 action for HCC cells.
PMID: 19624770 [PubMed - in process]

Endocr J. 2009;56(7):843-9. Epub 2009 Jun 24.

Vitamin K2 suppresses proliferation and motility of hepatocellular carcinoma cells by activating steroid and xenobiotic receptor.

Azuma K, Urano T, Ouchi Y, Inoue S.
Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

Vitamin K2, known as a cofactor for gamma-carboxylase, also serves as a ligand of a nuclear receptor, Steroid and Xenobiotic Receptor (SXR). Several clinical trials revealed that vitamin K2 reduced de novo formation and recurrence of hepatocellular carcinoma (HCC). To examine the role of SXR in HCC as a receptor activated by vitamin K2, the cells stably overexpressing SXR were established using a HCC cell line, HuH7. Overexpression of SXR resulted in reduced proliferation and motility of the cells. Further suppression of proliferation and motility was observed when SXR overexpressing clones were treated with vitamin K2. These results suggest that the activation of SXR could contribute to tumor suppressive effects of vitamin K2 on HCC cells.
PMID: 19550077 [PubMed - in process]

Cancer Lett. 2008 May 8;263(1):53-60. Epub 2008 Jan 30.

Vitamin K2 suppresses malignancy of HuH7 hepatoma cells via inhibition of connexin 43.

Kaneda M, Zhang D, Bhattacharjee R, Nakahama K, Arii S, Morita I.

Department of Cellular Physiological Chemistry, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8549, Japan.

The anti-cancer potential of vitamin K(2) (VK(2)) in hepatoma has gained considerable attention but the underlying mechanisms are unclear. Treatment of HuH7 hepatoma cells with VK(2) produced a normal liver phenotype. Following treatment of cells with VK(2), there was an increase in gap junctional intercellular communication activity, accompanied by up-regulation of connexin 32 (Cx32), dominantly expressed in normal hepatocyte. In contrast, Cx43 expression was inhibited. Moreover, the effect of VK(2) on Cx32 was abolished by over-expression of Cx43. Taken together, we propose that the anti-tumor effect of VK(2) is at least partly due to a decrease in Cx43 promoter activity.

PMID: 18249064 [PubMed - indexed for MEDLINE

J Gastroenterol. 2009;44(3):228-35. Epub 2009 Feb 13.

Involvement of hepatoma-derived growth factor in the growth inhibition of hepatocellular carcinoma cells by vitamin K(2).

Yamamoto T, Nakamura H, Liu W, Cao K, Yoshikawa S, Enomoto H, Iwata Y, Koh N, Saito M, Imanishi H, Shimomura S, Iijima H, Hada T, Nishiguchi S.

Division of Hepatobiliary and Pancreatic Medicine, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo, 663-8501, Japan.

BACKGROUND: Vitamin K(2) has been reported to suppress the growth of human hepatocellular carcinoma (HCC) in vitro and hepatocarcinogenesis in hepatitis C virus (HCV)-related cirrhosis in vivo. Hepatoma-derived growth factor (HDGF) is a unique nuclear targeting growth factor that is highly expressed in HCC cells and is a possible prognostic factor for patients with HCC. We investigated the regulation of HDGF expression by vitamin K(2). METHODS: Three HCC-derived cell lines, HepG2, HuH-7, and SK-Hep-1, were used. Cell number was determined with the MTT assay. The expression levels of HDGF mRNA and protein were measured by the real-time reverse transcriptase-polymerase chain reaction (PCR) method and ELISA and Western blot analysis, respectively. The HDGF promoter activity was measured by a dual luciferase-reporter assay. RESULTS: Vitamin K(2) suppressed the growth of the three HCC cell lines in a dose-dependent manner. Vitamin K(2) significantly suppressed the expression of the HDGF protein and mRNA in three cell lines. By a luciferase assay, vitamin K(2) significantly suppressed the promoter activity of the HDGF protein. Based on some luciferase-reporter plasmids containing truncated promoter regions, the possible responsive site of vitamin K(2) seems to reside in the region -1 to -150 bp of the HDGF gene. CONCLUSIONS: These findings suggested that regulation of the HDGF gene expression is one of the crucial mechanisms of vitamin K(2)-induced cell growth suppression for HCC.

PMID: 19214667 [PubMed - indexed for MEDLINE]

Chemotherapy. 2009;55(1):28-35. Epub 2008 Oct 31.

Vitamin K2 inhibits the growth of hepatocellular carcinoma via decrease of des-gamma-carboxy prothrombin.

Ma M, Qu XJ, Mu GY, Chen MH, Cheng YN, Kokudo N, Tang W, Cui SX.

Department of Pharmacology, School of Pharmaceutical Sciences, Shandong University, Jinan, China.

BACKGROUND: Des-gamma-carboxy prothrombin (DCP) is a serum protein produced by hepatocellular carcinoma (HCC) cells in the absence of vitamin K. Serum and tissue DCP expressions are thought to reflect the biological malignant potential of HCC. Hence, we aimed to examine the efficacy of vitamin K(2) on the production of DCP as well as tumor cell growth and invasion. METHODS: Cell growth and viability were evaluated by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assay. The in vivo efficacy of vitamin K(2) was examined in nude mice bearing HCC cells. A 24-well transwell chamber was used to evaluate the motility and invasive ability of HCC cells. Levels of DCP in supernatant of cultures and in serum of mice were measured using an electrochemiluminescence immunoassay method. Western blot and immunohistochemical analysis were employed to evaluate the expression of DCP in HCC. RESULTS: Vitamin K(2) (2-40 muM) significantly decreased the levels of DCP production in supernatant of PLC/PRF/5 and HepG2 cells and in serum of nude mice bearing HCC xenografts. The inhibition of DCP was also observed using the assays of Western blot analysis in HCC cultures and immunohistochemical analysis in HCC xenografts in mice. As a result of administration of vitamin K(2), the capacity of HCC growth was inhibited and the invasion and migration of tumor cells were decreased. Furthermore, the inhibitory effects of HCC growth were also observed in vivo and the sensitivity was well correlated with the decrease of DCP in the serum of mice. CONCLUSION: Vitamin K(2) might suppress the growth and invasion of HCC cells via decrease of DCP. (c) 2008 S. Karger AG, Basel.

PMID: 18974646 [PubMed - indexed for MEDLINE]

Vitam Horm. 2008;78:435-42.

Hepatocellular carcinoma and vitamin K.

Mizuta T, Ozaki I.

Department of Internal Medicine, Saga Medical School, 5-1-1 Nabeshima, Saga, Japan.

On the basis of reports of the antitumor effects of vitamin K on various cancers, we clinically investigated the suppressive effects of vitamin K2 on tumor recurrence after curative treatment for hepatocellular carcinoma (HCC). Our results showed that vitamin K2 administration significantly suppressed HCC recurrence. Our laboratory findings revealed that the inhibitory effect of vitamin K2 against HCC cell growth was generated by suppressing cyclin D1 expression through inhibition of NF-kappaB activation.

PMID: 18374204 [PubMed - indexed for MEDLINE]

Clin Calcium. 2007 Nov;17(11):1693-9.

[Clinical application of vitamin K for hepatocellular carcinoma]

[Article in Japanese]

Mizuta T, Ozaki I.

Saga Medical School, Department of Internal Medicine.

Despite recent progress in diagnosis and therapy, hepatocellular carcinoma (HCC) remains among the cancers with the poorest prognoses. Vitamin K (VK) have been shown to suppress the growth of HCC cells. Long-term administration of VK(2) has established its clinical safety, but it does not appear to exhibit marked anti-tumor effects when administered alone. For more effective use of VK against HCC, co-administration of VK(2) with other proven anticancer agents or development of a new VK preparation with a modified side-chain should be investigated in the future.

PMID: 17982189 [PubMed - indexed for MEDLINE]

Hepatol Res. 2007 Sep;37 Suppl 2:S303-7.

Potential role of vitamin K(2) as a chemopreventive agent against hepatocellular carcinoma.

Tamori A, Habu D, Shiomi S, Kubo S, Nishiguchi S.

Department of Hepatology, Osaka City University Graduate School of Medicine, Osaka, Japan.

Vitamin K, a cofactor necessary for the production of several antihemorrhagic factors, can inhibit the growth of various types of cells derived from neoplasms. In hepatoma cells, vitamin K(2) causes cell-cycle arrest and apoptosis. Vitamin K(2) is widely used in Japan to treat osteoporosis. The safety, relatively low cost and ease of use of vitamin K(2) have led to good compliance with treatment. The result of preliminary clinical trials in patients with chronic liver diseases are intriguing and suggest that vitamin K(2) might reduce the risk of hepatocellular carcinoma (HCC) in patients with liver cirrhosis as well as prevent disease recurrence after curative therapy in patients with HCC. This article reviews the potential role of vitamin K(2) as a chemopreventive agent against HCC and discusses future directions for clinical trials.

PMID: 17877500 [PubMed - in process]

Tohoku J Exp Med. 2007 Jul;212(3):335-9.

Vitamin K-deficient intracranial hemorrhage as the first symptom of cytomegalovirus hepatitis with cholestasis.

Yamada K, Fukao T, Suzuki H, Inoue R, Kondo T, Kondo N.

Department of Pediatrics, Graduate School of Medicine, Gifu University, Japan.

keitaro_ymd1976@yahoo.co.jp

Since vitamin K2 (VitK2) syrup prophylaxis has become a routine measure for neonates and young infants, the incidence of vitamin K deficiency (VitK-D) in infancy has markedly decreased. However, we recently experienced 2 infantile cases of VitK deficiency, in whom intracranial hemorrhage (ICH) was the first clinical sign of CMV hepatitis. Case 1 is a breast-fed boy who received VitK2 syrup orally at birth and at the age of 1 month. He did not suckle well and developed a generalized tonic convulsion twice at the age of 8 weeks. Case 2 is a mixed-fed boy who also received VitK2 syrup twice but developed vomiting and drowsiness at the age of 4 months. In both cases, laboratory tests showed anemia, leukocytosis, liver dysfunction with cholestasis, and coagulopathy, consistent with VitK-D abnormality. Their serological analyses showed that cytomegalovirus (CMV) IgG and IgM were both positive. In case 1, CMV DNA was positive, as judged by the PCR method. In case 2, CMV antigenemia was positive. Hence we diagnosed these two patients as having VitK-D ICH caused by CMV hepatitis with cholestasis. CMV hepatitis is a risk factor of VitK-D ICH.

PMID: 17592220 [PubMed - indexed for MEDLINE]

Intern Med. 2007;46(11):711-5. Epub 2007 Jun 1.

Hepatocellular carcinoma with peritoneal dissemination which was regressed during vitamin K2 and vitamin E administration.

Otsuka T, Hagiwara S, Tojima H, Yoshida H, Takahashi T, Nagasaka K, Tomioka S, Ando T, Takeuchi K, Kori T, Ohno Y, Kakizaki S, Takagi H, Mori M.

Department of Internal Medicine, Tone Chuo Hospital, Numata. tcht-otsuka@tonehoken.or.jp

A 65-year-old man with positive anti-hepatitis C antibody and chronic renal failure was diagnosed as having a ruptured hepatocellular carcinoma (HCC) based on computed tomography (CT). The patient underwent transcatheter arterial embolization (TAE) for the HCC. After one more session of TAE, the patient underwent surgery. But HCC seeding peritoneally was pointed out. Vitamin K2 and vitamin E were administered as a conservative treatment. Six months after starting vitamins K2 and E, the primary tumor did not increase in size and intraperitoneal dissemination disappeared on CT with a significant decrease of alpha-fetoprotein. Even though this is only one case, combination therapy of vitamin K2 and E may induce growth suppression of HCC.

PMID: 17541221 [PubMed - indexed for MEDLINE]

J Hepatol. 2007 Jul;47(1):83-92. Epub 2007 Feb 27.

Prevention of hepatocarcinogenesis with phosphatidylcholine and menaquinone-4: in vitro and in vivo experiments.

Sakakima Y, Hayakawa A, Nagasaka T, Nakao A.

Department of Surgery II, Nagoya University School of Medicine, Nagoya, Aichi, Japan.

sakakima@med.nagoya-u.ac.jp

BACKGROUND/AIMS: We examined whether phosphatidylcholine inhibited growth of hepatic cancer, as previously shown for menaquinone-4 (vitamin K2). METHODS: Growth inhibitions by phosphatidylcholine and/or menaquinone-4 and apoptosis induction by phosphatidylcholine were evaluated in vitro using human hepatic cancer cell lines (Hep-3B, Hep-G2, HuH-7, and Alexander). Effects of these agents were then investigated in male Sprague-Dawley rats against hepatocarcinogenesis induced by diethylnitrosamine plus phenobarbital. All rats were killed to examine livers to evaluate inhibitory potential macroscopically and immunohistochemically using an antibody against the marker of carcinogenesis, glutathione S-transferase and apoptotic induction by phosphatidylcholine using TUNEL staining. Blood samples were obtained by cardiac puncture. RESULTS: In vitro, phosphatidylcholine and menaquinone-4 each inhibited cancer cell growth and phosphatidylcholine induced apoptosis dose-dependently. Moreover, exposure to both synergistically inhibited growth in Hep-3B. In vivo, diets containing phosphatidylcholine with or without menaquinone-4 significantly reduced the number of macroscopic hepatic tumor nodules and the extent of abnormally immunoreactive foci conserving hepatic function on serum examinations compared with controls given only the carcinogens. Moreover, phosphatidylcholine supplementation induced apoptosis on TUNEL staining of liver sections. CONCLUSIONS: Given together, phosphatidylcholine and menaquinone-4 may exhibit synergy against hepatocarcinogenesis conserving hepatic function that could benefit patients at high risk for hepatocellular carcinoma.

PMID: 17399847 [PubMed - indexed for MEDLINE]

J Gastroenterol Hepatol. 2007 Apr;22(4):518-22.

Preventive effects of vitamin K on recurrent disease in patients with hepatocellular carcinoma arising from hepatitis C viral infection.

Kakizaki S, Sohara N, Sato K, Suzuki H, Yanagisawa M, Nakajima H, Takagi H, Naganuma A, Otsuka T, Takahashi H, Hamada T, Mori M.

Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan. kakizaki@showa.gunma-u.ac.jp

BACKGROUND: Despite the progression of therapeutic approaches, a high frequency of recurrence is what determines the long-term prognosis of patients with hepatocellular carcinoma (HCC). In this study, the chemopreventive effects of vitamin K2 on the recurrence and survival of patients with HCC after curative therapy were evaluated. METHODS: Sixty patients who were diagnosed to be free of HCC after radiofrequency ablation therapy or surgery were randomly assigned to either the vitamin K2 group (n = 30 patients) or the control group (n = 30 patients). All patients were positive for the hepatitis C virus (HCV) antibody and hepatitis B surface antigen positive patients were excluded from this study. Patients in the vitamin K2 group received an oral dose of menatetrenone at 45 mg per day. Disease recurrence and the survival rates were analyzed in patients with HCC. RESULTS: The cumulative recurrence-free rates in the vitamin K2 group were 92.3% at 12 months, 48.6% at 24 months and 38.8% at 36 months; and those in the control group were 71.7%, 35.9% and 9.9%, respectively (P = 0.045). The cumulative survival rates in the vitamin K2 group were 100% at 12 months, 95.0% at 24 months and 77.5% at 36 months; and those in the control group were 95.8%, 90.2% and 66.4%, respectively (P = 0.70). CONCLUSIONS: Vitamin K2 may have a suppressive effect on the recurrence of HCC and a beneficial effect on tumor recurrence. However, there was no significant difference in the survival rates. The chemopreventive effects of vitamin K2 are not sufficient. The development of a further regimen such as combination therapy is required.

PMID: 17376044 [PubMed - indexed for MEDLINE]

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Synergistic growth inhibition by acyclic retinoid and vitamin K2 in human hepatocellular carcinoma cells.

Kanamori T, Shimizu M, Okuno M, Matsushima-Nishiwaki R, Tsurumi H, Kojima S, Moriwaki H.

Department of Medicine, Gifu University School of Medicine, Gifu, Japan.

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide. However, effective chemopreventive and chemotherapeutic agents for this cancer have not yet been developed. In clinical trials acyclic retinoid (ACR) and vitamin K(2) (VK(2)) decreased the recurrence rate of HCC. In the present study we examined the possible combined effects of ACR or another retinoid 9-cis retinoic acid (9cRA) plus VK(2) in the HuH7 human HCC cell line. We found that the combination of 1.0 microM ACR or 1.0 microM 9cRA plus 10 microM VK(2) synergistically inhibited the growth of HuH7 cells without affecting the growth of Hc normal human hepatocytes. The combined treatment with ACR plus VK(2) also acted synergistically to induce apoptosis in HuH7 cells. Treatment with VK(2) alone inhibited phosphorylation of the retinoid X receptor (RXR)alpha protein, which is regarded as a critical factor for liver carcinogenesis, through inhibition of Ras activation and extracellular signal-regulated kinase phosphorylation. Moreover, the inhibition of RXRalpha phosphorylation by VK(2) was enhanced when the cells were cotreated with ACR. The combination of retinoids plus VK(2) markedly increased both the retinoic acid receptor responsive element and retinoid X receptor responsive element promoter activities in HuH7 cells. Our results suggest that retinoids (especially ACR) and VK(2) cooperatively inhibit activation of the Ras/MAPK signaling pathway, subsequently inhibiting the phosphorylation of RXRalpha and the growth of HCC cells. This combination might therefore be effective for the chemoprevention and chemotherapy of HCC.

PMID: 17270033 [PubMed - indexed for MEDLINE]

Int J Oncol. 2006 Dec;29(6):1501-8.

Apoptosis of liver cancer cells by vitamin K2 and enhancement by MEK inhibition.

Matsumoto K, Okano J, Nagahara T, Murawaki Y.

Second Department of Internal Medicine, Tottori University School of Medicine, Yonago, Tottori 683-8504, Japan.

Vitamin K2 (VK2) is an anti-proliferative agent toward a variety of cancer including hepatocellular carcinoma (HCC). Because the growth inhibitory effect of VK2 to HCC has not been established yet, we investigated it in HCC cells in vitro. VK2 inhibited growth of Hep3B, but not of HepG2, HLF, and Huh6. VK2 induced the cell cycle arrest at the G1 phase and involvement of apoptosis was suggested because the sub-G1 fraction appeared in flow cytometric analysis and nuclear condensation and fragmentation appeared after VK2 treatment. VK2 activated extracellular signal-regulated kinase (ERK)1/2 in a mitogen-activated ERK-regulating kinase (MEK)-dependent manner in Hep3B and Huh6, but not in HepG2 and HLF. When ERK1/2 was inhibited by U0126, apoptosis by VK2 in Hep3B, but not in Huh6, was significantly enhanced. However, Western blot analysis revealed that neither apoptosis induction by VK2 nor enhancement of apoptosis by U0126 was mediated by caspase activation. These data demonstrated that VK2 induced apoptosis and activated the MEK/ERK1/2 signaling pathway in a cell-type specific manner, and a MEK inhibitor could augment the cell death in these cells.

PMID: 17088989 [PubMed - indexed for MEDLINE]

Int J Oncol. 2005 Mar;26(3):713-20.

Antitumor effects of vitamins K1, K2 and K3 on hepatocellular carcinoma in vitro and in vivo.

Hitomi M, Yokoyama F, Kita Y, Nonomura T, Masaki T, Yoshiji H, Inoue H, Kinekawa F, Kurokohchi K, Uchida N, Watanabe S, Kuriyama S.

Third Department of Internal Medicine, Kagawa University School of Medicine, Kagawa 761-0793, Japan.

A number of studies have shown that various K vitamins, specifically vitamins K2 and K3, possess antitumor activity on various types of rodent- and human-derived neoplastic cell lines. In the present study, we examined the antitumor effects of vitamins K1, K2 and K3 on PLC/PRF/5 human hepatocellular carcinoma (HCC) cells in vitro and in vivo. Furthermore, we examined the mechanisms of antitumor actions of these vitamins in vitro and in vivo. Although vitamin K1 did not inhibit proliferation of PLC/PRF/5 cells at a 90-microM concentration (the highest tested), vitamins K2 and K3 suppressed proliferation of the cells at concentrations of 90 and 9 microM, respectively. By flow cytometric analysis, it was shown that not only vitamin K1, but also vitamin K2 did not induce apoptosis or cell cycle arrest on PLC/PRF/5 cells. In contrast, vitamin K3 induced G1 arrest, but not apoptosis on PLC/PRF/5 cells. Subsequent in vivo study using subcutaneous HCC-bearing athymic nude mice demonstrated that both vitamins K2 and K3 markedly suppressed the growth of HCC tumors to similar extent. Protein expression of cyclin D1 and cyclin-dependent kinase 4 (Cdk4), but not p16INK4a Cdk inhibitor in the tumor was significantly reduced by vitamin K2 or K3 treatment, indicating that vitamins K2 and K3 may induce G1 arrest of cell cycle on PLC/PRF/5 cells in vivo. Taken collectively, vitamins K2 and K3 were able to induce potent antitumor effects on HCC in vitro and in vivo, at least in part, by inducing G1 arrest of the cell cycle. The results indicate that vitamins K2 and K3 may be useful agents for the treatment of patients with HCC.

PMID: 15703828 [PubMed - indexed for MEDLINE]

Br J Nutr. 2002 Apr;87(4):307-14.

Difference in the metabolism of vitamin K between liver and bone in vitamin K-deficient rats.

Sato T, Ohtani Y, Yamada Y, Saitoh S, Harada H.

Chemicals Research Laboratories, Honen Corporation, Iwata-gun, Shizuoka, Japan. tosato@honen.co.jp

The difference between vitamin K metabolism in the liver and that in the bone of vitamin K-deficient rats was examined. After 17 d administration of vitamin K-deficient food, vitamin K in the liver was almost depleted, and prothrombin time (PT) was prolonged. Serum total osteocalcin level was slightly decreased by vitamin K deficiency, whereas serum undercarboxylated osteocalcin level did not change. The level of menaquinone (MK)-4 as well as that of phylloquinone was decreased, but approximately 40 % of the initial level still existed in the femur after the 17 d period. A single-dose administration of vitamin K (250 nmol/kg body weight) markedly increased vitamin K level in the liver but not in the femur. These results suggest that the turnover of vitamin K in the bone is slower than that in the liver, and bone metabolism may be little affected by the short period of intake of vitamin K-deficient food. However, intake of a larger amount of vitamin K is required for its accumulation in the bone than in the liver. Furthermore, the counteracting effect of MK-7 on prolonged PT in vitamin K-deficient rats was found to be higher than phylloquinone or MK-4.

PMID: 12064340 [PubMed - indexed for MEDLINE]

Vitamin K2 as a Cardioprotective

J Nutr. 2004 Nov;134(11):3100-5.

Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study.

Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, van der Meer IM, Hofman A, Witteman JC.
Department of Epidemiology & Biostatistics, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands.

Vitamin K-dependent proteins, including matrix Gla-protein, have been shown to inhibit vascular calcification. Activation of these proteins via carboxylation depends on the availability of vitamin K. We examined whether dietary intake of phylloquinone (vitamin K-1) and menaquinone (vitamin K-2) were related to aortic calcification and coronary heart disease (CHD) in the population-based Rotterdam Study. The analysis included 4807 subjects with dietary data and no history of myocardial infarction at baseline (1990-1993) who were followed until January 1, 2000. The risk of incident CHD, all-cause mortality, and aortic atherosclerosis was studied in tertiles of energy-adjusted vitamin K intake after adjustment for age, gender, BMI, smoking, diabetes, education, and dietary factors. The relative risk (RR) of CHD mortality was reduced in the mid and upper tertiles of dietary menaquinone compared to the lower tertile [RR = 0.73 (95% CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively]. Intake of menaquinone was also inversely related to all-cause mortality [RR = 0.91 (0.75, 1.09) and 0.74 (0.59, 0.92), respectively] and severe aortic calcification [odds ratio of 0.71 (0.50, 1.00) and 0.48 (0.32, 0.71), respectively]. Phylloquinone intake was not related to any of the outcomes. These findings suggest that an adequate intake of menaquinone could be important for CHD prevention.
PMID: 15514282 [PubMed - indexed for MEDLINE]

Nutr Metab Cardiovasc Dis. 2009 Sep;19(7):504-10. Epub 2009 Jan 28.

A high menaquinone intake reduces the incidence of coronary heart disease.

Gast GC, de Roos NM, Sluijs I, Bots ML, Beulens JW, Geleijnse JM, Witteman JC, Grobbee DE, Peeters PH, van der Schouw YT.
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands. g.c.m.gast@umcutrecht.nl

BACKGROUND AND AIM: Vitamin K dependent proteins have been demonstrated to inhibit vascular calcification. Data on the effect of vitamin K intake on coronary heart disease (CHD) risk, however, are scarce. To examine the relationship between dietary vitamins K(1) and K(2) intake, and its subtypes, and the incidence of CHD. METHODS AND RESULTS: We used data from the Prospect-EPIC cohort consisting of 16,057 women, enrolled between 1993 and 1997 and aged 49-70 years, who were free of cardiovascular diseases at baseline. Intake of vitamin K and other nutrients was estimated with a food frequency questionnaire. Multivariate Cox proportional hazards models were used to analyse the data. After a mean+/-SD follow-up of 8.1+/-1.6 years, we identified 480 incident cases of CHD. Mean vitamin K(1) intake was 211.7+/-100.3 microg/d and vitamin K(2) intake was 29.1+/-12.8 microg/d. After adjustment for traditional risk factors and dietary factors, we observed an inverse association between vitamin K(2) and risk of CHD with a Hazard Ratio (HR) of 0.91 [95% CI 0.85-1.00] per 10 microg/d vitamin K(2) intake. This association was mainly due to vitamin K(2) subtypes MK-7, MK-8 and MK-9. Vitamin K(1) intake was not significantly related to CHD. CONCLUSIONS: A high intake of menoquinones, especially MK-7, MK-8 and MK-9, could protect against CHD. However, more research is necessary to define optimal intake levels of vitamin K intake for the prevention of CHD.
PMID: 19179058 [PubMed - indexed for MEDLINE]

Am J Health Syst Pharm. 2005 Aug 1;62(15):1574-81.

Vitamin K in the treatment and prevention of osteoporosis and arterial calcification.

Adams J, Pepping J.
Castle Medical Center, Kailua, HI 96814, USA.

PURPOSE: The role of vitamin K in the prevention and treatment of osteoporosis and arterial calcification is examined. SUMMARY: Vitamin K is essential for the activation of vitamin K-dependent proteins, which are involved not only in blood coagulation but in bone metabolism and the inhibition of arterial calcification. In humans, vitamin K is primarily a cofactor in the enzymatic reaction that converts glutamate residues into gamma-carboxyglutamate residues in vitamin K-dependent proteins. Numerous studies have demonstrated the importance of vitamin K in bone health. The results of recent studies have suggested that concurrent use of menaquinone and vitamin D may substantially reduce bone loss. Menaquinone was also found to have a synergistic effect when administered with hormone therapy. Several epidemiologic and intervention studies have found that vitamin K deficiency causes reductions in bone mineral density and increases the risk of fractures. Arterial calcification is an active, cell-controlled process that shares many similarities with bone metabolism. Concurrent arterial calcification and osteoporosis have been called the "calcification paradox" and occur frequently in postmenopausal women. The results of two dose-response studies have indicated that the amount of vitamin K needed for optimal gamma-carboxylation of osteocalcin is significantly higher than what is provided through diet alone and that current dosage recommendations should be increased to optimize bone mineralization. Few adverse effects have been reported from oral vitamin K. CONCLUSION: Phytonadione and menaquinone may be effective for the prevention and treatment of osteoporosis and arterial calcification.
PMID: 16030366 [PubMed - indexed for MEDLINE]

Thromb Res. 2008;122(3):411-7. Epub 2008 Jan 30.

Effects of the blood coagulation vitamin K as an inhibitor of arterial calcification.

Wallin R, Schurgers L, Wajih N.
Department of Internal Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157, USA. rwallin@wfubmc.edu

INTRODUCTION: The transformation of smooth muscle cells (VSMCs) in the vessel wall to osteoblast like cells is known to precede arterial calcification which may cause bleeding complications. The vitamin K-dependent protein MGP has been identified as an inhibitor of this process by binding BMP-2, a growth factor known to trigger the transformation. In this study, we determined if the vitamin K-dependent Gla region in MGP by itself can inhibit the growth factor activity of BMP-2 and if menaquinone-4 (MK4) regulates gene expression in VSMCs. MATERIALS AND METHODS: A synthetic gamma-carboxyglutamic acid (Gla) containing peptide covering the Gla region in human MGP was used to test its ability to inhibit BMP-2 induced transformation of mouse pro-myoblast C2C12 cells into osteoblasts. MK4 was tested by microarray analysis as a gene regulatory molecule in VSMCs. RESULTS AND CONCLUSIONS: The results show that the Gla - but not the Glu-peptide inhibited the transformation which provide evidence that the Gla region in MGP is directly involved in the BMP-2/MGP interaction and emphasizes the importance of the vitamin K-dependent modification of MGP. From the data obtained from the microarray analysis, we focused on two quantitatively altered cDNAs representing proteins known to be associated with vessel wall calcification. DT-diaphorase of the vitamin K-cycle, showed increased gene expression with a 4.8-fold higher specific activity in MK4 treated cells. Osteoprotegrin gene expression was down regulated and osteoprotegrin protein secretion from the MK4 treated cells was lowered to 1.8-fold. These findings suggest that MK4 acts as an anti-calcification component in the vessel wall.
PMID: 18234293 [PubMed - indexed for MEDLINE]

Thromb Res. 2008;122(3):411-7. Epub 2008 Jan 30.

Effects of the blood coagulation vitamin K as an inhibitor of arterial calcification.

Wallin R, Schurgers L, Wajih N.

Department of Internal Medicine, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, North Carolina 27157, USA. rwallin@wfubmc.edu

INTRODUCTION: The transformation of smooth muscle cells (VSMCs) in the vessel wall to osteoblast like cells is known to precede arterial calcification which may cause bleeding complications. The vitamin K-dependent protein MGP has been identified as an inhibitor of this process by binding BMP-2, a growth factor known to trigger the transformation. In this study, we determined if the vitamin K-dependent Gla region in MGP by itself can inhibit the growth factor activity of BMP-2 and if menaquinone-4 (MK4) regulates gene expression in VSMCs. MATERIALS AND METHODS: A synthetic gamma-carboxyglutamic acid (Gla) containing peptide covering the Gla region in human MGP was used to test its ability to inhibit BMP-2 induced transformation of mouse pro-myoblast C2C12 cells into osteoblasts. MK4 was tested by microarray analysis as a gene regulatory molecule in VSMCs. RESULTS AND CONCLUSIONS: The results show that the Gla - but not the Glu-peptide inhibited the transformation which provide evidence that the Gla region in MGP is directly involved in the BMP-2/MGP interaction and emphasizes the importance of the vitamin K-dependent modification of MGP. From the data obtained from the microarray analysis, we focused on two quantitatively altered cDNAs representing proteins known to be associated with vessel wall calcification. DT-diaphorase of the vitamin K-cycle, showed increased gene expression with a 4.8-fold higher specific activity in MK4 treated cells. Osteoprotegrin gene expression was down regulated and osteoprotegrin protein secretion from the MK4 treated cells was lowered to 1.8-fold. These findings suggest that MK4 acts as an anti-calcification component in the vessel wall.

PMID: 18234293 [PubMed - indexed for MEDLINE]

J Atheroscler Thromb. 2007 Dec;14(6):317-24. Epub 2007 Dec 17.

Treatment with vitamin k(2) combined with bisphosphonates synergistically inhibits calcification in cultured smooth muscle cells.

Saito E, Wachi H, Sato F, Sugitani H, Seyama Y.
Department of Clinical Chemistry, Hoshi University School of Pharmacy and Pharmaceutical Sciences, Japan.

AIM: Vascular calcification is a common feature in patients with advanced atherosclerosis, postmenopausal women and patients with renal failure, which results in reduced elasticity of arteries. Pamidronate, a bisphosphonate, is used as a therapeutic agent for anti-osteoporosity, although there are adverse side effects, such as renal damage and aortic inflamed plaque rupture. In the present study, we demonstrated the effects of vitamin K(2) alone or in combination with pamidronate in an arterial calcification model induced using inorganic phosphate in cultured bovine aortic smooth muscle cells (BASMCs). METHODS: Calcification was induced by the addition of Pi (3 mM) in BASMCs. Calcium deposition was determined by Calcium C-test Wako and von Kossa staining. mRNA expression was assessed by semi-quantitative reverse transcription-polymerase chain reaction. RESULTS: Calcium deposition assay and von Kossa staining showed that calcification could be inhibited in a dose-dependent manner by treatment with vitamin K(2) alone, and that its inhibitory effect was enhanced when combined with pamidronate. It was found that the expression of tropoelastin mRNA was synergistically enhanced by combined treatment with vitamin K(2) and pamidronate, and the expression matrix Gla protein mRNA and osteopontin mRNA expression were also enhanced and suppressed, respectively, by treatment with vitamin K(2) or pamidronate. Moreover, our data showed that the suppression of TE expression by siRNA significantly increased Pi-induced vascular calcification. CONCLUSION: Taken together, our study suggests that vitamin K(2) in combination with pamidronate synergistically inhibits arterial calcification via the increased expression of tropoelastin, which would be a useful marker for developing effective therapeutic or prophylactic agents for arterial calcification.
PMID: 18174662 [PubMed - indexed for MEDLINE]

Z Kardiol. 2001;90 Suppl 3:57-63.

Role of vitamin K and vitamin K-dependent proteins in vascular calcification.

Schurgers LJ, Dissel PE, Spronk HM, Soute BA, Dhore CR, Cleutjens JP, Vermeer C.
Department of Biochemistry, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands.

OBJECTIVES: To provide a rational basis for recommended daily allowances (RDA) of dietary phylloquinone (vitamin K1) and menaquinone (vitamin K2) intake that adequately supply extrahepatic (notably vascular) tissue requirements. BACKGROUND: Vitamin K has a key function in the synthesis of at least two proteins involved in calcium and bone metabolism, namely osteocalcin and matrix Gla-protein (MGP). MGP was shown to be a strong inhibitor of vascular calcification. Present RDA values for vitamin K are based on the hepatic phylloquinone requirement for coagulation factor synthesis. Accumulating data suggest that extrahepatic tissues such as bone and vessel wall require higher dietary intakes and have a preference for menaquinone rather than for phylloquinone. METHODS: Tissue-specific vitamin K consumption under controlled intake was determined in warfarin-treated rats using the vitamin K-quinone/epoxide ratio as a measure for vitamin K consumption. Immunohistochemical analysis of human vascular material was performed using a monoclonal antibody against MGP. The same antibody was used for quantification of MGP levels in serum. RESULTS: At least some extrahepatic tissues including the arterial vessel wall have a high preference for accumulating and using menaquinone rather than phylloquinone. Both intima and media sclerosis are associated with high tissue concentrations of MGP, with the most prominent accumulation at the interface between vascular tissue and calcified material. This was consistent with increased concentrations of circulating MGP in subjects with atherosclerosis and diabetes mellitus. CONCLUSIONS: This is the first report demonstrating the association between MGP and vascular calcification. The hypothesis is put forward that undercarboxylation of MGP is a risk factor for vascular calcification and that the present RDA values are too low to ensure full carboxylation of MGP.
PMID: 11374034 [PubMed - indexed for MEDLINE]

Atherosclerosis. 2009 Apr;203(2):489-93. Epub 2008 Jul 19.

High dietary menaquinone intake is associated with reduced coronary calcification.

Beulens JW, Bots ML, Atsma F, Bartelink ML, Prokop M, Geleijnse JM, Witteman JC, Grobbee DE, van der Schouw YT.
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands. J.Beulens@umcutrecht.nl

BACKGROUND: Dietary vitamin K is thought to decrease risk of cardiovascular disease by reducing coronary calcification, but inconsistent results are reported. This may be due to different effects of vitamin K(1) (phylloquinone) and vitamin K(2) (menaquinone, MK), but few studies included both. METHODS: We investigated the association of intake of phylloquinone and menaquinone, including its subtypes (MK4-MK10), with coronary calcification in a cross-sectional study among 564 post-menopausal women. Phylloquinone and menaquinone intake was estimated using a food-frequency questionnaire. RESULTS: Sixty-two percent (n=360) of the women had coronary calcification based on 1.5-mm thick slices. Phylloquinone intake was not associated with coronary calcification with a relative risk (RR) of 1.17 (95%-confidence interval: 0.96-1.42; p(trend)=0.11) of the highest versus lowest quartile. Menaquinone intake was associated with decreased coronary calcification with an RR of 0.80 (95%-CI: 0.65-0.98; p(trend)=0.03). CONCLUSION: This study shows that high dietary menaquinone intake, but probably not phylloquinone, is associated with reduced coronary calcification. Adequate menaquinone intakes could therefore be important to prevent cardiovascular disease.
PMID: 18722618 [PubMed - indexed for MEDLINE]

Jpn J Pharmacol. 1997 Oct;75(2):135-43.

Effects of vitamin K2 (menatetrenone) on atherosclerosis and blood coagulation in hypercholesterolemic rabbits.

Kawashima H, Nakajima Y, Matubara Y, Nakanowatari J, Fukuta T, Mizuno S, Takahashi S, Tajima T, Nakamura T.
Pharmacological Evaluation Section, Tokyo Research Laboratoires, Eisai Co., Ltd., Koishikawa, Japan.

Gamma-Carboxyglutamic acid (Gla)-containing protein, synthesized in the presence of vitamin K, has been found in atherogenic plaques, but the pharmacological effect of vitamin K on atherosclerosis is unclear. We examined whether vitamin K2 (menatetrenone) could affect the progression of both atherosclerosis and hypercoagulability in hypercholesterolemic rabbits. Vitamin K2 in daily doses of 1, 10 and 100 mg/kg was given with a 0.5% cholesterol diet for 10 weeks to 8 rabbits each. The plasma levels of total-cholesterol in the vitamin K2-treated groups were clearly lower than that of the hypercholesterolemic control group. The excessive dose of vitamin K2, even at the high dose of 100 mg/kg/day for 10 weeks, did not accelerate the progression of atherosclerosis and did not promote the coagulative tendency in the rabbits. In contrast, the vitamin K2 treatment (1 to 10 mg/kg/day) suppressed the progression of atherosclerotic plaques, intima-thickening and pulmonary atherosclerosis, the increase of ester-cholesterol deposition in the aorta, and both the elevation in plasma factor X level and increase in Hepaplastin test value in the rabbits. These results indicate that the pharmacological dose of vitamin K2 prevents both the progression of atherosclerosis and the coagulative tendency by reducing the total-cholesterol, lipid peroxidation and factor X activity in plasma, and the ester-cholesterol deposition in the aorta in hypercholesterolemic rabbits.
PMID: 9414028 [PubMed - indexed for MEDLINE]

Vitamin K2 and Bone Health

Nutr Rev. 2008 Oct;66(10):549-57.

Update on the role of vitamin K in skeletal health.

Shea MK, Booth SL.

Vitamin K Laboratory, USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111, USA.

A protective role for vitamin K in bone health has been suggested based on its role as an enzymatic cofactor. In observational studies, vitamin K insufficiency is generally associated with lower bone mass and increased hip fracture risk. However, these findings are not supported in randomized controlled trials (RCT) of phylloquinone (vitamin K(1)) supplementation and bone loss at the hip in the elderly. This suggests that increased vegetable and legume intakes may simultaneously improve measures of vitamin K status and skeletal health, even though the mechanisms underlying these improvements may be independent of each other. Menaquinone-4 (vitamin K(2)), when given at pharmacological doses, appears to protect against fracture risk and bone loss at the spine. However, there are emerging data that suggest the efficacy of vitamin K supplementation on bone loss is inconclusive.

PMID: 18826451 [PubMed - indexed for MEDLINE]

Role of vitamin K2 in the treatment of postmenopausal osteoporosis.

Curr Drug Saf. 2006 Jan;1(1):87-97.
Iwamoto J, Takeda T, Sato Y.
Department of Sports Medicine, Keio University School of Medicine, Tokyo, Japan.
jiwamoto@sc.itc.keio.ac.jp

Vitamin K2, raloxifene, and bisphosphonates, such as etidronate, alendronate, and risedronate, are widely used in the treatment of postmenopausal osteoporosis in Japan. A meta-analysis study has demonstrated the efficacy of anti-resorptive agents: raloxifene and etidronate have been shown to reduce the incidence of vertebral fractures, and alendronate and risedronate have been shown to reduce the incidence of both vertebral and hip fractures. Furthermore, a report of the World Health Organization (WHO) has provided evidence from a randomized controlled trial suggesting that vitamin K2, which may stimulate bone formation via gamma-carboxylation of osteocalcin and/or steroid and xenobiotic receptors (SXRs), reduces the incidence of vertebral fractures, despite having only modest effects on the bone mineral density (BMD). Based on the weight of the currently available evidence, it is recommended that alendronate and risedronate, rather than vitamin K2, should be chosen initially for the treatment of postmenopausal osteoporosis, because these agents have been shown to be the most efficacious for reducing the incidence of both vertebral and hip fractures among the current range of commercially available agents. However, the more potent anti-fracture efficacy of combined treatment with the anti-resorptive and commercially available anabolic agents may need to be established. Some studies have shown that combined treatment with a bisphosphonate and vitamin K2 may be more effective than treatment with a bisphosphonate alone in preventing vertebral fractures. On the other hand, the results of a preclinical study do suggest the possible efficacy of combined treatment with vitamin K2 and raloxifene in the prevention of vertebral and hip fractures in postmenopausal women, although no clinical studies have reported on the effects of combined treatment with vitamin K2 and raloxifene in postmenopausal women with osteoporosis. Vitamin K deficiency, as indicated by high serum levels of undercarboxylated osteocalcin, has been shown to contribute to the occurrence of hip fractures in elderly women. Thus, we propose that the important role of vitamin K2 used in combination with bisphosphonates or raloxifene should not be underestimated in the prevention of fractures in postmenopausal women with osteoporosis with vitamin K deficiency.
PMID: 18690918 [PubMed - indexed for MEDLINE]

Curr Opin Clin Nutr Metab Care. 2001 Nov;4(6):483-7.

Effects of vitamin K on calcium and bone metabolism.

Zittermann A.

Department of Nutrition Science, University of Bonn, Germany. a.zittermann@uni-bonn.de

The K vitamins, a group of napthoquinones, are required for the carboxylation of a limited number of proteins including the bone matrix protein osteocalcin. Vitamin K1 (phylloquinone) and vitamin K2 (menaquinones), differ regarding food source (green vegetables and fermented products, respectively), bioavailability and intermediate metabolism. Epidemiological studies provide evidence for an association between a low vitamin K intake and an enhanced osteoporotic fracture risk. Doses of vitamin K1 up to 15 times the current recommended dietary allowance have successfully been used to reduce the percentage of undercarboxylated osteocalcin in the circulation. Studies demonstrating clear beneficial effects on bone health, however, are still lacking. In contrast, therapy with very high pharmacological doses of the vitamin K2 menatetrenone has impressively been used to prevent further bone mineral loss and fracture risk in osteoporotic patients.

PMID: 11706280 [PubMed - indexed for MEDLINE]

Curr Pharm Des. 2004;10(21):2557-76.

Effects of vitamin K2 on osteoporosis.

Iwamoto J, Takeda T, Sato Y.
Department of Sports Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. jiwamoto@sc.itc.keio.ac.jp

Vitamin K2 is a cofactor of gamma-carboxylase, which converts the glutamic acid (Glu) residue in osteocalcin molecules to gamma-carboxyglutamic acid (Gla), and is, therefore, essential for gamma-carboxylation of osteocalcin. Available evidence suggests that vitamin K2 also enhances osteocalcin accumulation in the extracellular matrix of osteoblasts in vitro. Osteocalcin-knockout mice develop hyperostosis, suggesting that the Gla-containing osteocalcin promotes normal bone mineralization. Although the precise role of osteocalcin in bone mineralization remains obscure, it probably regulates the growth of hydroxyapatite crystals. Furthermore, vitamin K2 also inhibits the expression of the osteoclast differentiation factor (ODF)/RANK ligand, tartrate-resistant acid phosphatase activity, and mononuclear cell formation, and induces osteoclast apoptosis in vitro. There is some evidence indicating that vitamin K2 prevents bone resorption in ovariectomized rats, retards the increase in bone turnover in orchidectomized rats, ameliorates the increase in bone resorption and decrease in bone formation in sciatic neurectomized rats, and prevents the decrease in bone formation in glucocorticoid-treated rats. These findings suggest that vitamin K2 may not only stimulate bone formation but also suppress bone resorption in vivo. Clinically, vitamin K2 sustains the lumbar bone mineral density (BMD) and prevents osteoporotic fractures in patients with age-related osteoporosis, prevents vertebral fractures in patients with glucocorticoid-induced osteoporosis, increases the metacarpal BMD in the paralytic upper extremities of patients with cerebrovascular disease, and sustains the lumbar BMD in patients with liver-dysfunction-induced osteoporosis. Vitamin K deficiency, as indicated by an increased circulating level of undercarboxylated osteocalcin, may contribute to osteoporotic fractures. Even though the effect of vitamin K2 on the BMD is quite modest, this vitamin may have the potential to regulate bone metabolism and play a role in reducing the risk of osteoporotic fractures. No randomized well-controlled prospective studies conducted on a sufficiently large number of patients have been reported yet, therefore, further studies are needed to confirm the efficacy of vitamin K2 in the treatment of osteoporosis.
PMID: 15320745 [PubMed - indexed for MEDLINE]

Altern Med Rev. 2005 Mar;10(1):24-35.

Vitamin K2 in bone metabolism and osteoporosis.

Plaza SM, Lamson DW.
Oncology Department, Bastyr University, Kenmore, Washington, USA.

This article covers in vitro, in vivo, and human data on the positive effect of vitamin K2 on osteoporosis. Data is available on vitamin K2 for osteoporosis caused by a number of conditions, including postmenopausal osteoporosis, Parkinson's disease, biliary cirrhosis, stroke, and drug-induced osteoporosis. The activity of vitamin K2 involves both an increase in the bone-building process and a separate decrease in the bone-loss process. Vitamin K2 exerts a more powerful influence on bone than vitamin K1, and should be considered for prevention or treatment in those conditions known to contribute to osteoporosis.

Clin Calcium. 2007 Nov;17(11):1727-30.

Treatment of primary osteoporosis with vitamin K2

[Article in Japanese]
Hosoi T.
National Center for Geriatrics and Gerontology, Department of Advanced Medicine.

Menatetrenone (MK-4) is a form of vitamin K(2) (VK(2)) which is utilized for the treatment of osteoporosis. MK4 has a grade B as a total recommendation rate in the Japanese guideline for the prevention and treatment of osteoporosis in 2006 based on the current clinical evidences. The effects of fracture prevention by MK-4 are assumed to be based on the increase of bone mineral density as well as the improvement of bone quality. Recent researches suggest that VK affects bone metabolism via nuclear receptor in addition to the carboxylation of VK dependent proteins.
PMID: 17982193 [PubMed - indexed for MEDLINE]

J Bone Miner Metab. 2005;23(1):41-7.

Vitamin K2 inhibits glucocorticoid-induced bone loss partly by preventing the reduction of osteoprotegerin (OPG).

Sasaki N, Kusano E, Takahashi H, Ando Y, Yano K, Tsuda E, Asano Y.
Department of Nephrology, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Tochigi 329-0498, Japan. eishun@jichi.ac.jp

We have recently demonstrated that glucocorticoid (GC) suppresses bone formation and enhances bone resorption, with resultant bone loss. This altered bone turnover is not due to the action of parathyroid hormone (PTH), but appears to be related to the suppression of osteoprotegerin (OPG). As vitamin K2 (menatetrenone) has been used for the treatment of osteoporosis, the present study was carried out to evaluate the effect of vitamin K2 on GC-induced bone loss. Twenty patients with chronic glomerulonephritis treated with GC for the first time were chosen for this study. Ten patients received GC alone (group A) and the other 10 patients each received 15 mg of vitamin K2 per day in addition to GC (group B). Markers of bone metabolism, including serum OPG, osteocalcin (OC), bone-specific alkaline phosphatase activity (BAP), PTH, tartrate-resistant acid phosphatase (TRAP), and bone mineral density (BMD), were measured before and during the treatment. OPG was significantly decreased in group A ($P < 0.001$), while no significant change was seen in group B. TRAP was markedly increased in both groups, more particularly in group A ($P < 0.01$). PTH was decreased in group A, but was increased in group B. OC was decreased at month 1 but subsequently increased until month 12 in both groups. BAP had decreased at month 3 in group A ($P < 0.05$), but not in group B. BMD of the lumbar spine was significantly reduced after 6 months ($P < 0.01$), and 12 months ($P < 0.001$) of treatment in group A, whereas there was no remarkable change in group B. The present study demonstrated that the inhibition exerted by vitamin K2 of the reduction in OPG induced by GC may, at least in part, play a role in the prevention and treatment of GC-induced bone loss.
PMID: 15616893 [PubMed - indexed for MEDLINE]

Br J Nutr. 2009 May 19:1-8. [Epub ahead of print]

The effect of menaquinone-7 (vitamin K2) supplementation on osteocalcin carboxylation in healthy prepubertal children.

van Summeren MJ, Braam LA, Lilien MR, Schurgers LJ, Kuis W, Vermeer C.

Department of Paediatrics, University Medical Centre Utrecht, PO Box 85090, 3508 AB Utrecht, The Netherlands.

Vitamin K contributes to bone health, probably through its role as cofactor in the carboxylation of osteocalcin. Intervention studies in adults have demonstrated that markedly higher osteocalcin carboxylation is obtained by intakes of vitamin K well above the current recommended dietary intake. However, the relationship between increased vitamin K2 intake and enhanced osteocalcin carboxylation has never been shown in healthy children. The objective was to study the effect of 45 mug menaquinone-7 (MK-7; one of the vitamin K2 species) on the circulating levels of undercarboxylated osteocalcin (ucOC) and carboxylated osteocalcin (cOC) in healthy prepubertal children. We hypothesised that MK-7 supplementation will reduce the ucOC:cOC ratio (UCR), indicating an improved vitamin K status. The present study is a double-blind randomised placebo-controlled trial examining the effect of 8 weeks MK-7 supplementation on the carboxylation of osteocalcin in healthy children (n 55). Serum levels of ucOC, cOC and MK-7 were measured at baseline and after 8 weeks, together with bone markers and coagulation parameters. The UCR was used as an indicator of vitamin K status. In the MK-7-supplemented group (n 28), the circulating concentration of inactive ucOC reduced and the UCR improved whereas the concentration of MK-7 increased. Within the placebo group, ucOC, cOC, UCR and MK-7 did not significantly change over time. In both groups, bone markers and coagulation parameters remained constant over time. These findings demonstrate that in healthy, prepubertal children, modest supplementation with MK-7 increases circulating concentrations of MK-7 and increases osteocalcin carboxylation.

PMID: 19450370 [PubMed - as supplied by publisher]

Clin Calcium. 2007 Nov;17(11):1678-84.

Related Articles, Links

[Vitamin K and bone quality]

[Article in Japanese]

Hara K, **Akiyama Y**.

Eisai Co., Ltd., Clinical Research Center, Applied Drug Research Department, Pharmacological Evaluation Section.

Meta-analysis involving previous clinical studies showed that VK(2) decreased the incidence of fracture. In particular, the results based on the data on bone mineral density and fracture suggested that VK(2) improves bone quality. Preclinical studies regarding bone quality reported that VK(2) improved the trabecular microarchitecture (connectivity and width) in an ovariectomized model, and that VK(2) increased the bone strength without influencing the bone mineral content in a model fed a low-Mg diet and a vitamin C deficiency model, increasing the collagen level and proline hydroxylation. Thus, improvement in bone quality via actions on the bone geometry and collagen level/quality may be involved in a VK(2)-related decrease in the incidence of new fracture in clinical studies.

Publication Types:

- English Abstract
- Review

PMID: 17982187 [PubMed - indexed for MEDLINE]

Clin Calcium. 2005 Apr;15(4):605-10.

Vitamin K2 as a protector of bone health and beyond

[Article in Japanese]
Kaneki M.
Department of Anesthesia & Critical Care, Signal Transduction Laboratory
Massachusetts General Hospital, Harvard Medical School, USA.

Several lives of evidence indicate a protective effect of vitamin K against osteoporosis. Epidemiological studies showed that low vitamin K intake is associated with the increased risk of osteoporosis. Vitamin K2 (menatetrenone, MK-4) has been clinically used in the treatment of patients with osteoporosis in Japan, Korea and Thailand. Previous studies demonstrated the efficacy of vitamin K2 (45 mg/day) to prevent bone loss and reduce the rate of vertebral fractures, although a large, randomized intervention study is anticipated to provide more detailed evidence. Recently, vitamin K2 has been shown to reduce the progression of hepatocarcinoma. Moreover, it has been proposed that vitamin K may also have beneficial effects to prevent atherogenesis. The clarification of molecular mechanisms by which vitamin K2 exerts these salutary effects deserve further investigations.
PMID: 15802772 [PubMed - indexed for MEDLINE]

Clin Calcium. 2005 Jun;15(6):1034-9.

Vitamin K2 (menatetrenone) and bone quality

[Article in Japanese]
Iinuma N.
Department of marketed product research clinical research center, Eisai Co., Ltd.

Vitamin K2 (menatetrenone) treatment was reported to significantly prevent new clinical fracture (chi2 = 10.935;p = 0.0273) in a 2-year group comparison study of patients with osteoporosis, although it only maintained the baseline bone mineral density. This result strongly suggested that another factor was involved in promoting bone strength apart from an increase in bone mineral density. With respect to the therapeutic effect of menatetrenone treatment on corticosteroid-induced osteoporosis over 2 years, the incidence of a new vertebral fracture was 13.3% in the menatetrenone treatment group versus 41% in the control group, indicating that this treatment could prevent fractures. Multivariate logistic regression analysis was performed to investigate independent risk factors for new vertebral fractures, and treatment with menatetrenone showed a preventive effect on fracture with an odds ratio of 0.03 and a risk rate of 0.003.
PMID: 15930719 [PubMed - indexed for MEDLINE]

Clin Calcium. 2007 Nov;17(11):1738-44.

Vitamin K2 as a potential therapeutic agent for glucocorticoid-induced osteoporosis

[Article in Japanese]
Tanaka I, Oshima H.
Fujita Health University, Department of Clinical and Laboratory Medicine.

In recent years, bone quality is thought to be an important factor in bone strength. Vitamin K(2) (VK(2))drugs inhibit bone fracture, although their effect of increasing bone mineral density (BMD)is lower compared to bisphosphonate. This suggests VK(2) analogs improve bone quality. Glucocorticoid-induced osteoporosis(GIOP)brings about a bone fracture even under the condition of high BMD. VK(2) drugs might be effective to prevent bone fracture in GIOP, because they increase bone strength independently of bone mineral density (BMD).
PMID: 17982195 [PubMed - indexed for MEDLINE]

J Orthop Sci. 2000;5(6):546-51.

Effect of combined administration of vitamin D3 and vitamin K2 on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis.

Iwamoto J, Takeda T, Ichimura S.
Department of Sports Clinic, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.

The effect of the combined administration of vitamin D3 and vitamin K2 on bone mineral density (BMD) of the lumbar spine was examined in postmenopausal women with osteoporosis. Ninety-two osteoporotic women who were more than 5 years after menopause, aged 55-81 years, were randomly divided into four administration groups: vitamin D3 (1alpha hydroxyvitamin D3, 0.75 microg/day) (D group; n = 29), vitamin K2 (menatetrenone, 45 mg/day) (K group; n = 22), vitamin D3 plus vitamin K2 (DK group, n = 21), and calcium (calcium lactate, 2 g/day) (C group; n = 20). BMD of the lumbar spine (L2-L4) was measured by dual energy X-ray absorptiometry at 0, 1, and 2 years after the treatment started. There were no significant differences in age, body mass index, years since menopause, and initial BMD among the four groups. One-way analysis of variance (ANOVA) with repeated measurements showed a significant decrease in BMD in the C group ($P < 0.001$). Two-way ANOVA with repeated measurements showed a significant increase in BMD in the D and K groups compared with that in the C group ($P < 0.05$ and $P < 0.001$, respectively), and a significant increase in BMD in the DK group compared with that in the C, D, and K groups ($P < 0.0001$, $P < 0.05$ and $P < 0.01$, respectively). These findings indicate that combined administration of vitamin D3 and vitamin K2, compared with calcium administration, appears to be useful in increasing the BMD of the lumbar spine in postmenopausal women with osteoporosis.
PMID: 11180916 [PubMed - indexed for MEDLINE]

Osteoporos Int. 2007 Jul;18(7):963-72. Epub 2007 Feb 8.

Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women.

Knapen MH, Schurgers LJ, Vermeer C.
CARIM, University of Maastricht, Maastricht, The Netherlands.

SUMMARY: Vitamin K mediates the synthesis of proteins regulating bone metabolism. We have tested whether high vitamin K(2) intake promotes bone mineral density and bone strength. Results showed that K(2) improved BMC and femoral neck width, but not DXA-BMD. Hence high vitamin K(2) intake may contribute to preventing postmenopausal bone loss. INTRODUCTION: Vitamin K is involved in the synthesis of several proteins in bone. The importance of K vitamins for optimal bone health has been suggested by population-based studies, but intervention studies with DXA-BMD as a clinical endpoint have shown contradicting results. Unlike BMC, DXA-BMD does not take into account the geometry (size, thickness) of bone, which has an independent contribution to bone strength and fracture risk. Here we have tested whether BMC and femoral neck width are affected by high vitamin K intake. METHODS: A randomized clinical intervention study among 325 postmenopausal women receiving either placebo or 45 mg/day of vitamin K(2) (MK-4, menatetrenone) during three years. BMC and hip geometry were assessed by DXA. Bone strength indices were calculated from DXA-BMD, femoral neck width (FNW) and hip axis length (HAL). RESULTS: K(2) did not affect the DXA-BMD, but BMC and the FNW had increased relative to placebo. In the K(2)-treated group hip bone strength remained unchanged during the 3-year intervention period, whereas in the placebo group bone strength decreased significantly. CONCLUSIONS: Vitamin K(2) helps maintaining bone strength at the site of the femoral neck in postmenopausal women by improving BMC and FNW, whereas it has little effect on DXA-BMD.
PMID: 17287908 [PubMed - indexed for MEDLINE]

Clin Calcium. 2009 Dec;19(12):1805-14.

Anti-fracture efficacy of vitamin K

[Article in Japanese]
Iwamoto J.
Institute for Integrated Sports Medicine, Keio University School of Medicine, Japan.

The objective of the present review of the literature was to evaluate the effect of vitamin K supplementation on the skeleton of postmenopausal women. PubMed was used to search the reliable literature for randomized controlled trials (RCTs) by using the inclusion criteria: >or= approximately 50 subjects per group and study period of >or= 2 years. The results of 7 RCTs that met the inclusion criteria showed that vitamin K (K(1) and K(2)) supplementation reduced serum undercarboxylated osteocalcin levels regardless of dose, but that it had inconsistent effects on serum total osteocalcin levels and no effect on bone resorption. Despite the lack of a significant change or the occurrence of only a modest increase in bone mineral density, high-dose vitamin K supplementation improved indices of bone strength in the femoral neck and reduced the incidence of clinical fractures. Furthermore, a post hoc analysis in a large RCT in Japan showed that high-dose vitamin K(2) supplementation decreased the subsequent incidence of vertebral fractures in osteoporotic postmenopausal women with a history of at least 5 vertebral fractures. The review of the reliable literature showed the effect of high-dose vitamin K supplementation on the skeleton of postmenopausal women mediated by mechanisms other than bone mineral density and bone turnover.
PMID: 19949272 [PubMed - in process]

Br J Nutr. 2009 Oct;102(8):1171-8. Epub 2009 May 19.

The effect of menaquinone-7 (vitamin K2) supplementation on osteocalcin carboxylation in healthy prepubertal children.

van Summeren MJ, Braam LA, Lilien MR, Schurgers LJ, Kuis W, Vermeer C.
Department of Paediatrics, University Medical Centre Utrecht, PO Box 85090, 3508 AB Utrecht, The Netherlands. m.j.h.vansummeren@umcutrecht.nl

Vitamin K contributes to bone health, probably through its role as cofactor in the carboxylation of osteocalcin. Intervention studies in adults have demonstrated that markedly higher osteocalcin carboxylation is obtained by intakes of vitamin K well above the current recommended dietary intake. However, the relationship between increased vitamin K2 intake and enhanced osteocalcin carboxylation has never been shown in healthy children. The objective was to study the effect of 45 microg menaquinone-7 (MK-7; one of the vitamin K2 species) on the circulating levels of undercarboxylated osteocalcin (ucOC) and carboxylated osteocalcin (cOC) in healthy prepubertal children. We hypothesised that MK-7 supplementation will reduce the ucOC:cOC ratio (UCR), indicating an improved vitamin K status. The present study is a double-blind randomised placebo-controlled trial examining the effect of 8 weeks MK-7 supplementation on the carboxylation of osteocalcin in healthy children (n 55). Serum levels of ucOC, cOC and MK-7 were measured at baseline and after 8 weeks, together with bone markers and coagulation parameters. The UCR was used as an indicator of vitamin K status. In the MK-7-supplemented group (n 28), the circulating concentration of inactive ucOC reduced and the UCR improved whereas the concentration of MK-7 increased. Within the placebo group, ucOC, cOC, UCR and MK-7 did not significantly change over time. In both groups, bone markers and coagulation parameters remained constant over time. These findings demonstrate that in healthy, prepubertal children, modest supplementation with MK-7 increases circulating concentrations of MK-7 and increases osteocalcin carboxylation.
PMID: 19450370 [PubMed - indexed for MEDLINE]

J Nutr Sci Vitaminol (Tokyo). 2009 Feb;55(1):15-21.

Effect of low dose vitamin K2 (MK-4) supplementation on bio-indices in postmenopausal Japanese women.

Koitaya N, Ezaki J, Nishimuta M, Yamauchi J, Hashizume E, Morishita K, Miyachi M, Sasaki S, Ishimi Y.

Nutritional Epidemiology Program, National Institute of Health and Nutrition, 1-23-1, Toyama, Shinjyuku-ku, Tokyo 162-8636, Japan.

It has been reported that treatment with a pharmacological dose (45 mg/d) of menaquinone-4 (MK-4) prevents bone loss in postmenopausal women. However, it is not known whether supplementation with low dose MK-4 has beneficial effects on bone metabolism in healthy women. The aim of this study is to examine the effects of the supplementation of 1.5 mg/d MK-4 for 4 wk on bone and lipid metabolism in healthy postmenopausal Japanese women. The study was performed as a randomized double blind placebo-controlled trial. The participants aged 53-65 y were randomly assigned to 2 groups and supplemented with 1.5 mg/d of MK-4 or a placebo for 4 wk (n=20 for each group). The most marked effects of MK-4 intake were observed on serum osteocalcin (OC) concentrations. Serum undercarboxylated OC (ucOC) concentration decreased, and the gamma-carboxylated OC (GlaOC) and GlaOC/GlaOC+ucOC ratio that indicates the degree of OC gamma-carboxylation increased significantly at 2 and 4 wk compared with that at baseline in the MK-4 group. The serum ucOC and GlaOC concentrations in the MK-4 group were significantly different from those in the placebo group at 2 wk. These results suggest that supplementation with 1.5 mg/d MK-4 accelerated the degree of OC gamma-carboxylation. The concentrations of serum lipids and other indices were not different between the groups at either intervention period. Thus, the additional intake of MK-4 might be beneficial in the maintenance of bone health in postmenopausal Japanese women.

PMID: 19352059 [PubMed - indexed for MEDLINE]

Calcif Tissue Int. 2008 Aug;83(2):121-8. Epub 2008 Jun 10.

Effects of vitamin K(2) and risedronate on bone formation and resorption, osteocyte lacunar system, and porosity in the cortical bone of glucocorticoid-treated rats.

Iwamoto J, Matsumoto H, Takeda T, Sato Y, Liu X, Yeh JK.

Department of Sports Medicine, Keio University School of Medicine, Tokyo, Japan.

jiwamoto@sc.itc.keio.ac.jp

The purpose of the present study was to examine the effects of vitamin K(2) and risedronate on bone formation and resorption, the osteocyte lacunar system, and porosity in the cortical bone of glucocorticoid (GC)-treated rats. Forty-nine female Sprague-Dawley rats, 3 months of age, were randomized into five groups according to the following treatment schedule: age-matched control, GC administration, and GC administration with concomitant administration of vitamin K(2), risedronate, or vitamin K(2) + risedronate. At the end of the 8-week experiment, classical bone histomorphometric analysis was performed, and the osteocyte lacunar system and porosity were evaluated on the cortical bone of the tibial diaphysis. GC administration decreased percent cortical bone area and increased percent marrow area as a result of decreased periosteal bone formation, and increased endocortical bone erosion, and increased cortical porosity. Vitamin K(2) prevented a reduction in periosteal bone formation but did not affect percent cortical bone and marrow areas. Risedronate prevented a reduction in periosteal bone formation and an increase in endocortical bone erosion, resulting in prevention of alterations in percent cortical bone and marrow areas. Both vitamin K(2) and risedronate increased osteocyte density and lacunar occupancy and prevented a GC-induced increase in cortical porosity. Vitamin K(2) and risedronate had additive effects on osteocyte density and lacunar occupancy and a synergistic effect on cortical porosity. The present study showed the efficacy of vitamin K(2) and risedronate for bone formation and resorption, the osteocyte lacunar system, and porosity in the cortical bone of GC-treated rats.

PMID: 18543014 [PubMed - indexed for MEDLINE]

J Bone Miner Metab. 2008;26(3):260-4. Epub 2008 May 11.

Response of serum carboxylated and undercarboxylated osteocalcin to alendronate monotherapy and combined therapy with vitamin K2 in postmenopausal women.

Hirao M, Hashimoto J, Ando W, Ono T, Yoshikawa H.

Department of Orthopaedics, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka, 565-0871, Japan.

Alendronate decreases the risk of femoral neck fracture by suppressing bone turnover, and also decreases the serum total osteocalcin level. A low serum carboxylated osteocalcin level or high undercarboxylated osteocalcin level could be risk factors for femoral neck fracture. Vitamin K mediates the carboxylation of osteocalcin, but the effect of alendronate therapy with or without vitamin K(2) supplementation remains unknown. Forty-eight postmenopausal women were enrolled in a 1-year prospective randomized trial and assigned to alendronate monotherapy (5 mg/day) (group A, n = 26) or vitamin K(2) (45 mg/day) plus alendronate (5 mg/day) (group AK, n = 22). Bone mineral density was measured by dual-energy X-ray absorptiometry at 0 and 12 months; bone turnover parameters were measured at 0, 3, and 12 months. Four patients discontinued alendronate therapy, and we analyzed the remaining 44 patients (23 in group A and 21 in group AK) who completed 1 year of treatment. Alendronate decreased undercarboxylated osteocalcin; carboxylated osteocalcin was not affected. Addition of vitamin K(2) enhanced the decrease of undercarboxylated osteocalcin levels and led to a greater increase of femoral neck bone mineral density. Alendronate monotherapy does not decrease carboxylation of osteocalcin, and combination of vitamin K(2) and alendronate brings further benefits on both osteocalcin carboxylation and BMD of femoral neck in postmenopausal women with osteoporosis.

PMID: 18470667 [PubMed - indexed for MEDLINE]

Clin Calcium. 2007 Nov;17(11):1663-72.

[Vitamin K metabolism. Menaquinone-4 (MK-4) formation from ingested VK analogues and its potent relation to bone function]

[Article in Japanese]

Komai M, Shirakawa H.

Tohoku University, Graduate School of Agricultural Science, Department of Science of Food Function and Health, Laboratory of Nutrition.

Phylloquinone (vitamin K(1) = VK(1)) and the menaquinones (MK-n, or vitamin K(2) = VK(2)) are naturally occurring forms of VK. Most of the menaquinone series are synthesized by microorganisms, but we have reported that MK-4 is usual in being synthesized by the conversion of orally ingested VK(1) or MK-n in the major tissues of germfree rats and mice which lack their intestinal microflora. This result led us to deny 1960's Martius' hypothesis that described the participation of bacterial enzyme of the intestinal flora to this conversion. VK acts as a cofactor in the posttranslational synthesis of gamma-carboxyglutamic acid (Gla) from glutamic acid (Glu) residues in the nascent Gla-protein molecule. Therefore, VK is essential for blood coagulation (various clotting factors) and bone structure (as osteocalcin [OC = BGP] and matrix Gla-protein [MGP] in mammals. In addition to the liver, VK is found in the bone, brain, heart, testis, kidney, pancreas and salivary glands mainly as MK-4, and it has been reported that MK-4 itself has specific biological activities in these tissues beside Gla-protein formation. However, the physiological role of MK-4 in these organs has not been fully understood yet. Recently MK-4 has been attracted the attention of researchers due to its activities such as apoptotic activity on the osteoclast cells and leukemia cells, SXR/PXR ligand, and so on. We further review the potent important physiological role of MK-4 in the bone as well as other major tissues.

PMID: 17982185 [PubMed - indexed for MEDLINE]

SOD (Superoxide Dismutase)

Editors' Note: There has been much discussion about the human body's ability to assimilate SOD (Superoxide Dismutase) from the diet. Superoxide Dismutase is a potent free radical eliminator produced by the human body; however, due to increased levels of free radicals in modern life (due to a number of factors), most scientists feel that the human body's production of SOD is insufficient and increased dietary antioxidants and/or supplementation is necessary. SOD would serve as the perfect dietary antioxidant supplement; however, this fragile enzyme has not proven sturdy enough to withstand severe deterioration by stomach acids prior to assimilation.

Fortunately, Spirulina in tablet form is not fully digested in the stomach; only a portion of the Spirulina tablets are digested in the stomach, while a substantial amount of the tablets are then digested in the intestines. It appears evident then, that by taking Spirulina in tablet form, the SOD in the part of the tablets digested in the intestines (where there is no stomach acid present) should be assimilated by the human body.

SOD and Arthritis

Arthritis Rheum. 2005 Nov;52(11):3479-91.

Extracellular superoxide dismutase and oxidant damage in osteoarthritis.

Regan E, **Flannelly J**, **Bowler R**, **Tran K**, **Nicks M**, **Carbone BD**, **Glueck D**, **Heijnen H**, **Mason R**, **Crapo J**.

Department of Medicine, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, CO 80206, USA. regane@njc.org

OBJECTIVE: To use human cartilage samples and a mouse model of osteoarthritis (OA) to determine whether extracellular superoxide dismutase (EC-SOD) is a constituent of cartilage and to evaluate whether there is a relationship between EC-SOD deficiency and OA. METHODS: Samples of human cartilage were obtained from femoral heads at the time of joint replacement surgery for OA or femoral neck fracture. Samples of mouse tibial cartilage obtained from STR/ort mice and CBA control mice were compared at 5, 15, and 35 weeks of age. EC-SOD was measured by enzyme-linked immunosorbent assay, Western blotting, and immunohistochemistry techniques. Real-time quantitative reverse transcription-polymerase chain reaction was used to measure messenger RNA for EC-SOD and for endothelial cell, neuronal, and inducible nitric oxide synthases. Nitrotyrosine formation was assayed by Western blotting in mouse cartilage and by fluorescence immunohistochemistry in human cartilage. RESULTS: Human articular cartilage contained large amounts of EC-SOD (mean +/- SEM 18.8 +/- 3.8 ng/gm wet weight of cartilage). Cartilage from patients with OA had an approximately 4-fold lower level of EC-SOD compared with cartilage from patients with hip fracture. Young STR/ort mice had decreased levels of EC-SOD in tibial cartilage before histologic evidence of disease occurred, as well as significantly more nitrotyrosine formation at all ages studied. CONCLUSION: EC-SOD, the major scavenger of reactive oxygen species in extracellular spaces, is decreased in humans with OA and in an animal model of OA. Our findings suggest that inadequate control of reactive oxygen species plays a role in the pathophysiology of OA.

PMID: 16255039 [PubMed - indexed for MEDLINE]

Cell Transplant. 2008;17(12):1371-80.

The therapeutic effect of extracellular superoxide dismutase (EC-SOD) mouse embryonic fibroblast (MEF) on collagen-induced arthritis (CIA) mice.

Yu DH, **Kim MO**, **Kim SH**, **Shin MJ**, **Kim BS**, **Kim HJ**, **Lee SR**, **Lee SG**, **Yoo SA**, **Kim WU**, **Hyun BH**, **Park YS**, **Kim TY**, **Ryoo ZY**.

School of Life Sciences and Biotechnology, Kyungpook National University, Daegu 702-701, Korea.

Rheumatoid arthritis is a chronic inflammatory disease. The generation of reactive oxygen species (ROS) within an inflamed joint has been suggested as playing a significant pathogenic role. Extracellular superoxide dismutase (EC-SOD) is a major scavenger enzyme of ROS, which has received growing attention for its therapeutic potential. To investigate the therapeutic effect of EC-SOD in mice with collagen-induced arthritis (CIA), we used mouse embryonic fibroblast (MEF) of transgenic mice that overexpresses EC-SOD on the skin by using hK14 promoter. DBA/1 mice that had been treated with bovine type II collagen were administrated subcutaneous injections of EC-SOD transgenic MEF (each at 1.4 x 10(60 cells) on days 28, 35, and 42 after primary immunization. To test EC-SOD activity, blood samples were collected in each group on day 49. The EC-SOD activity was nearly 1.5-fold higher in the transgenic MEF-treated group than in the nontransgenic MEF-treated group ($p < 0.05$). The severity of arthritis in mice was scored in a double-blind manner, with each paw being assigned a separate clinical score. The severity of arthritis in EC-SOD transgenic MEF-treated mice was significantly suppressed in the arthritic clinical score ($p < 0.05$). To investigate the alteration of cytokine levels, ELISA was used to measure blood samples. Levels of IL-1beta and TNF-alpha were reduced in the transgenic MEF-treated group ($p < 0.05$). Abnormalities of the joints were examined by H&E staining. There were no signs of inflammation except for mild hyperplasia of the synovium in the transgenic MEF-treated group. The proliferation of CII-specific T cells was lower in the transgenic MEF-treated mice than in those in the other groups. The transfer of EC-SOD transgenic MEF has shown a therapeutic effect in CIA mice and this approach may be a safer and more effective form of therapy for rheumatoid arthritis.

Publication Types: Research Support, Non-U.S. Gov't

PMID: 19364074 [PubMed - in process]

J Control Release. 2005 Mar 21;103(2):419-34. Epub 2005 Jan 15.

Developments in the rat adjuvant arthritis model and its use in therapeutic evaluation of novel non-invasive treatment by SOD in Transfersomes.

Simões SI, **Delgado TC**, **Lopes RM**, **Jesus S**, **Ferreira AA**, **Morais JA**, **Cruz ME**, **Corvo ML**, **Martins MB**.

Unidade de Novas Formas de Agentes Bioactivos, Departamento de Biotecnologia, Instituto Nacional de Engenharia, Tecnologia e Inovação, Edifício F, Estrada do Paço do Lumiar, 22 1649-038 Lisboa, Portugal. sandra.simoes@ineti.pt

The aim of this study was firstly to refine a rat model of arthritis, the adjuvant arthritis (AA) model, by studying the time course of the disease, introducing new evaluation methods such as haematological and biochemical parameters in order to identify the main stages of the disease. An optimisation of treatment schedule and evaluation criteria was developed. This refinement provided novel non-invasive anti-inflammatory treatment of the AA with SOD by using mixed lipid vesicles specially developed for transdermal delivery, Transfersomes (Tfs), this being the second major aim. The time course of AA includes a first stage: 1 day after the disease induction, the induced paw volume more than doubled and the paw circumference increased by approx. 50%. Two weeks later, another stage occurred where the disease shifted from the local arthritis form towards polyarthritis: an additional increase of volume and circumference of the induced and non-induced paws, occurred. The animals also started to loose weight around day 14 after the disease induction. Radiographic observable lesions increased correspondingly. Treatment of animals, started at day 1 after induction, by epicutaneous application of SOD-Tfs showed that 1 mg SOD/kg body weight is more efficient than 0.66 mg SOD /kg body weight. As a positive control, SOD liposomes intravenously injected were used for comparison and confirmed the biological efficiency of epicutaneously applied SOD in Tfs. SOD solution and empty Tfs epicutaneously applied exerted no effect. In addition, epicutaneous application of SOD-Tfs used prophylactically was able to suppress the induced rat paw oedema. Radiographic images showed less joint lesions in SOD-Tfs treated animals in comparison with control and placebo treated rats. It was shown for the first time that SOD incorporated into Tfs and applied onto a skin area not necessarily close to the inflamed tissue is able to promote non-invasive treatment of induced arthritis.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15763624 [PubMed - indexed for MEDLINE]

Pol Merkur Lekarski. 2008 May;24(143):396-8.

[Activity of superoxide dismutase (CuZn-SOD) in erythrocytes of patients after hips alloplasty]

[Article in Polish]

Mrowicka M, **Garncarek P**, **Bortnik K**, **Gałecka E**, **Miller E**, **Smigielski J**.

Medical University of Lódź, The Faculty of Physiotherapy, Chair and Department of Chemistry and Clinical Biochemistry, Poland. mrowmal@o2.pl

Hip osteoarthritis leads, among others, to abnormally decreased physical activity (hypokinesia). Adverse effect of physical inactivity can cause inhibition of anabolic processes in favour of enhancement of protein, carbohydrate, and lipid catabolitic reactions, as well as inadequate metabolism of polyunsaturated fatty acids. These alterations can induce an increased lipid peroxide synthesis, overproduction of reactive oxygen species (ROS) and acceleration of lipid peroxidation processes. The aim of the study was to determine superoxide dismutase activity (CuZn-SOD) in red blood cells of patients suffering from hip osteoarthritis prior to and following total alloplasty as compared to healthy subjects, and also to evaluate effect of hypokinesia on oxidative stress. MATERIAL AND METHODS; CuZn-SOD activity in red blood cells was determined according to the Misra and Fridovich method in 36 patients with hip osteoarthritis hospitalized at the Traumatic-Orthopaedic Department of the Ministry of Internal Affairs and Administration Hospital in Lódź. RESULTS: In patients with decreased physical activity in ten days after alloplasty, enzyme activity increased (+24.9%), one month since the operation it decreased, but it higher as compared to result activity of CuZn-SOD prior to surgery (+16.8%). CONCLUSIONS: The results activity of superoxide dysmutase leads to ROS generation and their overgeneration in hip osteoarthritis and in first time of treatment.

Publication Types:

- English Abstract

PMID: 18634380 [PubMed - indexed for MEDLINE]

Scand J Rheumatol. 2008 Mar-Apr;37(2):103-8.

Increased levels of autoantibodies against catalase and superoxide dismutase associated with oxidative stress in patients with rheumatoid arthritis and systemic lupus erythematosus.

Mansour RB, **Lassoued S**, **Gargouri B**, **El Gaïd A**, **Attia H**, **Fakhfakh F**.

Units of Biotechnology and Pathology, Higher Institute of Biotechnology of Sfax, Sfax, Tunisia. riadhbm2004@yahoo.fr

OBJECTIVE: To evaluate the level of autoantibodies against superoxide dismutase (SOD) and catalase (CAT) in the sera of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) Tunisian patients, to study the oxidative profile among the same patients and to establish a correlation between the two parameters in order to understand the role of each one in the genesis of the two diseases. METHOD: Using a standard enzyme-linked immunosorbent assay (ELISA), the levels of immunoglobulin G (IgG) and IgM directed against CAT and SOD in the sera of 39 RA patients, 40 SLE patients, and 50 control healthy individuals were evaluated. The oxidative/antioxidative profile was tested by measuring serum malondialdehyde (MDA), conjugated dienes (CD), CAT activity, and SOD activity. RESULTS: Our data showed increased levels of IgG antibodies (Ab) against CAT in both groups of patients ($p<0.05$) compared to control subjects. However, the SLE patients displayed an increased level of anti-SOD IgG ($p<0.05$). In all patients the lipid peroxidation was confirmed by high levels of MDA and conjugated dienes ($p<0.05$). RA patients exhibited an increasing CAT and SOD activity in their sera ($p<0.05$) with a positive correlation observed between CAT and IgG anti-CAT ($p<0.05$). The same results were observed for SLE patients. In addition, a positive correlation was observed between anti-CAT Ab and anti-SOD Ab in SLE patients ($p<0.05$). CONCLUSION: Collectively, these results suggested that the primary factor causing the oxidative stress observed in RA and SLE is excessive free radical production rather than impaired CAT or SOD activity due to autoantibody inhibition.

PMID: 18415766 [PubMed - indexed for MEDLINE]

Joint Bone Spine. 2007 Jul;74(4):324-9. Epub 2007 May 24.

Reactive oxygen species and superoxide dismutases: role in joint diseases.

Afonso V, **Champy R**, **Mitrovic D**, **Collin P**, **Lomri A**.

INSERM U606, IFR-139, Paris 7 University, Lariboisière Teaching Hospital, 2 rue Ambroise Paré, 75475 Paris Cedex 10, France.

Reactive oxygen species (ROS) are produced in many normal and abnormal processes in humans, including atheroma, asthma, joint diseases, aging, and cancer. The superoxide anion O(2)(-) is the main ROS. Increased ROS production leads to tissue damage associated with inflammation. Superoxide dismutases (SODs) convert superoxide to hydrogen peroxide, which is then removed by glutathione peroxidase or catalase. Thus, SODs prevent the formation of highly aggressive ROS, such as peroxynitrite or the hydroxyl radical. Experimental models involving SOD knockout or overexpression are beginning to shed light on the pathophysiological role of SOD in humans. Although the antiinflammatory effects of exogenous native SOD (orgotein) are modest, synthetic SOD mimetics hold considerable promise for modulating the inflammatory response. In this review, we discuss new knowledge about the role of the superoxide anion and its derivates as mediators of inflammation and the role of SODs and SOD mimetics as antioxidant treatments in joint diseases such as rheumatoid arthritis, osteoarthritis, and crystal-induced arthropathies.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

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Targeted delivery of catalase and superoxide dismutase to macrophages using folate.

Lee S, **Murthy N**.

The Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA. slee60@mail.gatech.edu

Reactive oxygen species (ROS) secreted by activated macrophages play a central role in causing rheumatoid arthritis, and therapeutics that can inhibit the production of ROS by macrophages have great clinical potential. Superoxide dismutase (SOD) and catalase (CAT) are two enzymes that scavenge ROS and have great potential for treating rheumatoid arthritis. However, clinical trials with these enzymes have been ineffective, due to drug delivery problems, and effective SOD and CAT delivery vehicles are greatly needed. In this communication, we demonstrate that CAT and SOD can be effectively targeted to activated macrophages, via the folate receptor. Folate was conjugated to CAT and SOD using NHS/EDC chemistry with high efficiency. Cell culture experiments demonstrated that folate conjugation increased their ability to scavenge ROS, produced by the macrophages, and also enhanced their uptake into activated macrophages. We anticipate numerous applications of folate-conjugated CAT and SOD in treating inflammatory diseases, based on their efficacy and straightforward synthesis.

Publication Types:

- Research Support, N.I.H., Extramural
- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.

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J Control Release. 2007 Feb 12;117(2):186-95. Epub 2006 Nov 10.

Enzymosomes with surface-exposed superoxide dismutase: in vivo behaviour and therapeutic activity in a model of adjuvant arthritis.

Gaspar MM, **Boerman OC**, **Laverman P**, **Corvo ML**, **Storm G**, **Cruz ME**.

Unidade Novas Formas de Agentes Bioactivos, Departamento de Biotecnologia, Instituto Nacional de Engenharia Tecnologia e Inovação, IP, Estrada do Paço do Lumiar, 22, 1649-038 Lisboa, Portugal.

Acylated Superoxide Dismutase (Ac-SOD) enzymosomes, liposomal enzymatic systems expressing catalytic activity in the intact form, were previously characterized. The main scope of the present work was to investigate the biological behaviour of Ac-SOD inserted in the lipid bilayer of liposomes, in comparison with SOD located in the aqueous compartment of liposomes. Two types of liposomes were used: conventional liposomes presenting an unmodified external surface and long circulating liposomes coated with poly (ethylene glycol) (PEG). Liposomal formulations of Ac-SOD and SOD were prepared and labelled with indium-111 and their in vivo fate compared. Data obtained led us to the conclusion that, for liposomes coated with PEG the in vivo fate was not influenced by the insertion of Ac-SOD in the lipid bilayers. The potential therapeutic effect of Ac-SOD enzymosomes was compared with SOD liposomes in a rat model of adjuvant arthritis. A faster anti-inflammatory effect was observed for Ac-SOD enzymosomes by monitoring the volume of the inflamed paws. The present results allowed us to conclude that Ac-SOD enzymosomes are nano-carriers combining the advantages of expressing enzymatic activity in intact form and thus being able to exert therapeutic effect even before liposomes disruption, as well as acting as a sustained release of the enzyme.

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Arthritis Rheum. 2004 Nov;50(11):3702-11.

Enhancement of collagen-induced arthritis in mice genetically deficient in extracellular superoxide dismutase.

Ross AD, **Banda NK**, **Muggli M**, **Arend WP**.

National Jewish Medical and Research Center, Denver, Colorado, USA.

OBJECTIVE: To examine the influence of superoxide on the severity of collagen-induced arthritis (CIA) in mice. METHODS: CIA was induced in DBA/1J mice lacking the extracellular superoxide dismutase (EC-SOD) gene (knockout [KO]) and in normal DBA/1J mice (wild-type [WT]). RESULTS: The clinical disease activity score was significantly higher in EC-SOD-KO mice than in WT mice between days 36 and 53, and the histologic scores for joint damage on day 53 increased 2-fold or more in the EC-SOD-KO mice. There were no significant differences between the 2 groups of mice in proliferation indices of spleen or lymph node cells in vitro after stimulation with type II collagen. Although both IgG1 and IgG2a anticollagen antibody levels increased in both groups of mice between days 21 and 53, there were no significant differences between the 2 groups. Lipopolysaccharide-stimulated spleen cells from EC-SOD-KO mice produced greater levels of tumor necrosis factor alpha (TNFalpha) over 48 hours in culture compared with cells from WT mice. Increased steady-state levels of messenger RNA (mRNA) for interferon-gamma (IFNgamma), TNFalpha, and interleukin-1beta (IL-1beta), and lower levels of IL-1 receptor antagonist (IL-1Ra) mRNA were present in the joints of the EC-SOD-KO mice compared with the WT mice. CONCLUSION: The absence of EC-SOD leads to more severe CIA, which may be accompanied by enhanced production of the proinflammatory cytokines IFNgamma, TNFalpha, and IL-1beta, and decreased production of the antiinflammatory cytokine IL-1Ra in the joints.

Publication Types:

- Research Support, U.S. Gov't, P.H.S.

PMID: 15529385 [PubMed - indexed for MEDLINE]

Scand J Rheumatol. 2004;33(4):239-43.

Correlation between soluble intercellular adhesion molecule 1 level and extracellular superoxide dismutase activity in rheumatoid arthritis: a possible association with disease activity.

Ugur M, **Yildirim K**, **Kiziltunc A**, **Erdal A**, **Karatay S**, **Senel K**.

Department of Physical Medicine and Rehabilitation, Atatürk University, 25240 Erzurum, Turkey. mugur66@hotmail.com

OBJECTIVE: We investigated serum levels of soluble intercellular adhesion molecule-1 (sICAM-1) and the activity of extracellular superoxide dismutase (EC-SOD) in rheumatoid arthritis (RA). We also considered whether there was a correlation between sICAM-1 and EC-SOD and disease activity. METHODS: Levels of sICAM-1 were measured in serum from 42 patients with active RA and 30 control subjects by enzyme-linked immunosorbent assay (ELISA). EC-SOD activity was determined in sera isolated from patients with active RA and from controls. RESULTS: The serum levels of sICAM-1 were significantly higher in patients with RA than in control subjects ($p<0.001$). In contrast, the activity of EC-SOD was significantly lower in RA patients than in healthy controls ($p<0.001$). A significant negative correlation was found between the levels of sICAM-1 and EC-SOD activity ($r=-0.39$, $p<0.01$). There was a statistically positive correlation between sICAM-1 levels with Ritchie articular index (RAI) score and C-reactive protein (CRP) ($r=0.32$, $p<0.05$; $r=0.44$, $p<0.01$, respectively). CONCLUSIONS: These results show that the increased levels of sICAM-1 present in active RA patients might be due to the decreased activity of EC-SOD, and increased levels of sICAM-1 may also reflect disease status or activity.

PMID: 15370719 [PubMed - indexed for MEDLINE]

Postepy Hig Med Dosw (Online). 2004 Jul 24;58:301-11.

[Extracellular superoxide dismutase (EC-SOD)--structure, properties and functions]

[Article in Polish]

Skrzycki M, **Czeczot H**.

Katedra i Zakład Biochemii Akademii Medycznej w Warszawie.
skrzyckimp@poczta.onet.pl

EC-SOD catalyzes the dismutation of superoxide radical to hydrogen peroxide and oxygen in the interstitial spaces of tissues and in extracellular fluids (plasma, lymph, and synovial fluid). It eliminates superoxide radicals from the cell environment and prevents the formation of reactive oxygen species and their derivatives. EC-SOD is a secretory, tetrameric glycoprotein containing copper and zinc, with a high affinity to certain glycosaminoglycans, such as heparin and heparan sulfate. It plays an important role in maintaining vascular tone, lung function, and the metabolism of NO, and in the pathology of such diseases as atherosclerosis, diabetes, and arthritis. This paper describes EC-SOD structure, function in tissues, and possibilities of therapy with application of this enzyme.

Publication Types:

- English Abstract
- Review

PMID: 15280800 [PubMed - indexed for MEDLINE]

SOD and Skin Health

Biochem Biophys Res Commun. 2006 Sep 22;348(2):450-8. Epub 2006 Jul 28.

Inhibition of the TPA-induced cutaneous inflammation and hyperplasia by EC-SOD.

Ha HY, **Kim Y**, **Ryoo ZY**, **Kim TY**.

Department of Dermatology and Catholic Research Institute of Medical Science, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Seocho-gu, Seoul 137-040, Republic of Korea.

This study reports the roles of extracellular superoxide dismutase (EC-SOD) in the cutaneous inflammation and hyperplasia with 12-O-tetradecanoylphorbol-3-acetate (TPA) application in EC-SOD transgenic mice (Tg EC-SOD). Topical double TPA treatment induced the various inflammatory changes including the epidermal thickness, elevated the PCNA-labeling index, the edema formation, and increased production of hydrogen peroxide (H2O2) in wild type mice (WT). These changes were markedly suppressed in TPA-treated Tg EC-SOD. The expressions of the inflammatory cytokines, IL-1alpha and IL-1beta, were reduced in the TPA-treated Tg EC-SOD compared with those in TPA-treated WT. The expression of IL-1alpha was significantly increased in the skin of TPA-treated WT, especially in the basal and suprabasal layers, but it was restricted focally in basal layer of the skin of TPA-treated Tg EC-SOD. The number of infiltrating inflammatory cells and the IL-1beta expressing cells was obviously reduced in TPA-treated Tg EC-SOD in comparison with TPA-treated WT. The result suggests that EC-SOD might play an important role in the suppression of TPA-induced cutaneous inflammation and epidermal hyperplasia by regulating the expression of IL-1alpha and IL-1beta, although the mechanisms remain to be elucidated.

Publication Types:

- Research Support, Non-U.S. Gov't

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Biomed Pharmacother. 2005 May;59(4):209-14. Epub 2005 Mar 17.

Modulation of skin tumorigenesis by SOD.

St Clair D, **Zhao Y**, **Chaiswing L**, **Oberley T**.

Graduate Center for Toxicology, University of Kentucky, Lexington, KY 40536, USA. dtsc100@pop.uky.edu

Generation of reactive oxygen species (ROS) has been implicated in the development of cancer. Groundwork establishing mitochondria as a critical source of ROS generation and the role of manganese superoxide dismutase (MnSOD) in preventing mitochondria-mediated cell death have been well established. In a seemingly contradictory role, it also is well documented that increased MnSOD expression suppresses the carcinogenesis effect of ROS. Our recent studies demonstrated that overexpression of MnSOD reduced tumor incidence in the two-stage 7,12-dimethylbenz(a)-anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA) skin carcinogenesis model. However, reduction of MnSOD by heterozygous knockout of the MnSOD gene (Sod 2+/-) did not lead to an increase in tumor incidence. Thus, how modulation of mitochondrial ROS levels alter the outcome of developing cancer is unclear. This review will provide background information on the sequence of ROS-mediated events in the mitochondria and evidence that suggests that the antioxidant and tumor suppressor functions of MnSOD are indeed inter-related. It also will offer insights into the mechanisms by which MnSOD modulates the outcome of early stage skin carcinogenesis.

Publication Types:

- Review

PMID: 15862717 [PubMed - indexed for MEDLINE]

Indian J Dermatol Venereol Leprol. 2009 May-Jun;75(3):268-71.

Determination of oxidative stress in vitiligo by measuring superoxide dismutase and catalase levels in vitiliginous and non-vitiliginous skin.

Sravani PV, **Babu NK**, **Gopal KV**, **Rao GR**, **Rao AR**, **Moorthy B**, **Rao TR**.

Department of Dermatology, King George Hospital, Andhra University, Visakhapatnam, AP, India.

BACKGROUND: Vitiligo is an acquired disorder characterized by circumscribed depigmented macules devoid of identifiable melanocytes. Complex genetic, immunological, neural and self destructive mechanisms interplay in its pathogenesis. According to autocytotoxic hypothesis, oxidative stress has been suggested to be the initial pathogenic event in melanocyte degeneration. AIMS: The aim of our investigation was to evaluate the role of oxidative stress by measuring levels of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) in lesional and normal skin of patients with vitiligo and in the skin of normal controls. METHODS: We determined the activity of SOD in lesional and non-lesional skin and CAT in lesional skin only of 25 vitiligo patients and 25 controls by using the spectrophotometric assay and Aebi's method, respectively. RESULTS: There was statistically significant increase in the levels of SOD in vitiliginous and non vitiliginous skin of patient group compared to the control group ($P < 0.001$). No significant difference was found between the levels of SOD in lesional skin and non-lesional skin of vitiligo patients. The levels of CAT in the skin of patients were found to be significantly lower than those of controls ($P < 0.001$). CONCLUSIONS: There is increased oxidative stress in vitiligo as is indicated by high levels of SOD and low levels of CAT in the skin of vitiligo patients.

PMID: 19439879 [PubMed - in process]

J Burn Care Res. 2009 Mar-Apr;30(2):321-8.

Lecithinized superoxide dismutase suppresses free radical substrates during the early phase of burn care in rats.

Koizumi T, **Goto H**, **Tanaka H**, **Yamaguchi Y**, **Shimazaki S**.

Burn Care Unit, Division of Critical Care Medicine, Kyorin University Hospital, Mitaka City, Tokyo.

Severe hypovolemia is caused by an increase in blood vessel permeability in the early phase after an extensive burn; massive fluid volume replacement has been used for the treatment of this condition. The release of oxygen free radicals and chemical mediators, especially from skin tissue, induces the increase in blood vessel permeability. Free radical burst is associated with ischemia-related skin tissue injury. Although various antioxidant therapies have been used to inhibit the consequences of hypovolemia, an effective method has not been established. To elucidate the protective effects of lecithinized superoxide dismutase (PC-SOD) as an antioxidant agent. Each rat sustained a 30% total body surface area burn (n = 20) on the back by the Walker and Mason method were allocated into three groups: (1) no treatment group (n = 6), (2) a low dose of PC-SOD (0.67 mg/kg) group (n = 7), and (3) a high dose of PC-SOD (1.33 mg/kg) group (n = 7). The concentrations of malondialdehyde and SOD in the serum, skin tissue, and lung tissue were measured in each group 1 hour after burning. Both low and high doses of PC-SOD prevented malondialdehyde concentration associated with free radical burst after burning compared with the no treatment group ($P < .05$); serum (27.7 +/- 6.8, 10.8 +/- 2.7, and 12.1 +/- 2.8 nmol/L), skin tissue (2251.3 +/- 560.5, 802.7 +/- 228.8, and 790.1 +/- 188.3 nmol/wet.g), and lung (157.3 +/- 19.5, 109.1 +/- 23.9, and 81.9 +/- 20.3 nmol/wet.g). These data suggest that PC-SOD may be a protective agent against free radical-induced vasodilatation caused by severe, extensive burns.

PMID: 19242269 [PubMed - indexed for MEDLINE]

Biochem Pharmacol. 2008 Mar 15;75(6):1348-57. Epub 2007 Dec 3.

Topical transduction of superoxide dismutase mediated by HIV-1 Tat protein transduction domain ameliorates 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice.

Song HY, **Lee JA**, **Ju SM**, **Yoo KY**, **Won MH**, **Kwon HJ**, **Eum WS**, **Jang SH**, **Choi SY**, **Park J**.

Department of Biomedical Science, Hallym University, 1 Okchun-dong, Chunchon, Kangwon-Do 200-702, Republic of Korea.

A domain (RKKRRQRRR) derived from HIV-1 Tat is one of the most efficient protein transduction domains (PTD) for delivering macromolecules including proteins into cells and tissues. Antioxidant enzymes such as superoxide dismutase (SOD) and catalase are major cellular defenses against oxidative stress which results in various diseases including skin inflammation. In this study, we examined the effect of SOD fused with HIV-1 Tat PTD (Tat-SOD) on TPA-induced skin inflammation in mice. Topical application of Tat-SOD to mice ears 1h after TPA application once a day for 3 days dose-dependently inhibited TPA-induced ear edema in mice. Topical application on mice ears of Tat-SOD also suppressed TPA-induced expression of proinflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6 as well as cyclooxygenase-2 (COX-2) and production of PGE(2). Furthermore, topical application of Tat-SOD resulted in significant reduction in activation of NF-kappaB and mitogen-activated protein kinases (MAPK) in the mice ears treated with TPA. These data demonstrates that Tat-SOD inhibits TPA-induced inflammation in mice by reducing the levels of expression of proinflammatory cytokines and enzymes regulated by the NF-kappaB and MAPK and can be used as a therapeutic agent against skin inflammation related to oxidative damage.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18164693 [PubMed - indexed for MEDLINE]

Bull Exp Biol Med. 2006 Oct;142(4):447-9.

Antinecrotic and antioxidant effects of superoxide dismutase during skin ischemia.

[Article in English, Russian]

Galenko-Yaroshevskii VP, **Galka VV**, **Stoyalova ON**, **Agadzhanova AV**, **Lapina IV**, **Gaivoronskaya TV**, **Popkova LV**, **Churilova IV**, **Gorelashvili AS**, **Antelava NA**, **Berberashvili TM**, **Sukoyan GV**.

Krasnodar Branch, Southern Bureau of the Russian Academy of Medical Sciences, Kuban State Medical University, Krasnodar.

Antinecrotic activity of SOD was studied in rats with experimental skin ischemia. Treatment with SOD increased activity of endogenous SOD in skin homogenates (by 70 and 26% compared to the ischemic and intact skin, respectively). However, the rate of superoxide anion generation remained unchanged after SOD treatment. Creatine phosphate content and NAD/NADH redox potential increased by 16 and 21%, respectively, on day 3 after SOD administration. The increase in functional activity of the energy supply system and rise in the reserve capacity of the antioxidant protection system contribute to inhibition of lactate dehydrogenase and creatine phosphokinase and decrease in the cytolysis index under the influence of SOD. Our results indicate that SOD produces the antinecrotic effect and holds much promise for the therapy of skin ischemia.

PMID: 17415433 [PubMed - indexed for MEDLINE]

Eur J Pharm Biopharm. 2007 Jun;66(3):451-9. Epub 2006 Nov 26.

Assessment of physical and antioxidant activity stability, in vitro release and in vivo efficacy of formulations added with superoxide dismutase alone or in association with alpha-tocopherol.

Di Mambro VM, **Fonseca MJ**.

Department of Pharmaceutical Science, University of São Paolo, Ribeirão Preto, Brazil. valeriadimambro@yahoo.com.br

A topical formulation was added with different concentrations of superoxide dismutase (SOD) alone or in association with alpha-tocopherol (alpha-TOC). The physical stability was evaluated by rheological behavior of formulations stored at 4 degrees C, 30 degrees C/60% RH and 40 degrees C/70% RH for 6 months. SOD alone and formulations containing SOD 0.2%, 0.4% or 0.6% or SOD and alpha-TOC were stored in the same conditions and the enzymatic activity was evaluated by the superoxide anion scavenging using chemiluminescence measurement. In vitro release study was carried out using modified Franz diffusion cell and SOD formulations photoprotection against skin erythema was observed for 72 h. SOD and alpha-TOC formulation proved to be instable, since the interaction between the antioxidants led to both physical and enzymatic activity instability. SOD formulations showed to be physically stable and maintained the enzymatic activity for 6 months when stored at 4 and 30 degrees C/60% RH. Despite the fact of low SOD release from the formulation, it was effective in inhibiting the UVB-induced skin erythema for 48 h after a single application. Topical administration of antioxidants provides an efficient way to enrich the endogenous cutaneous protection system, and SOD formulations could be used for improving photoprotection of skin.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 17196809 [PubMed - indexed for MEDLINE]

Cancer Res. 2005 Feb 15;65(4):1401-5.

A mechanism-based antioxidant approach for the reduction of skin carcinogenesis.

Zhao Y, **Chaiswing L**, **Oberley TD**, **Batinic-Haberle I**, **St Clair W**, **Epstein CJ**, **St Clair D**.

Graduate Center for Toxicology and Department of Radiation Medicine, University of Kentucky, Lexington, Kentucky, USA.

Studies in our laboratories showed that overexpression of manganese superoxide dismutase (MnSOD) reduced tumor incidence in a multistage skin carcinogenesis mouse model. However, reduction of MnSOD by heterozygous knockout of the MnSOD gene (MnSOD KO) did not lead to an increase in tumor incidence, because a reduction of MnSOD enhanced both cell proliferation and apoptosis. The present study extends our previous studies in the MnSOD KO mice and shows that apoptosis in mouse epidermis occurred prior to cell proliferation (6 versus 24 hours) when treated with tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). To investigate the possibility that a timed administration of SOD following apoptosis but before proliferation may lead to suppression of tumor incidence, we applied a SOD mimetic (MnTE-2-PyP(5+)) 12 hours after each TPA treatment. Biochemical studies showed that MnTE-2-PyP(5+) suppressed the level of protein carbonyls and reduced the activity of activator protein-1 and the level of proliferating cellular nuclear antigen, without reducing the activity of p53 or DNA fragmentation following TPA treatment. Histologic examination confirmed that MnTE-2-PyP(5+) suppressed mitosis without interfering with apoptosis. Remarkably, the incidence and multiplicity of skin tumors were reduced in mice that received MnTE-2-PyP(5+) before cell proliferation. These results show a novel strategy for an antioxidant approach to cancer intervention.

Publication Types:

- Research Support, Non-U.S. Gov't
- Research Support, U.S. Gov't, Non-P.H.S.
- Research Support, U.S. Gov't, P.H.S.

PMID: 15735027 [PubMed - indexed for MEDLINE]

Exp Dermatol. 2004 Nov;13(11):691-9.

Extracellular superoxide dismutase tissue distribution and the patterns of superoxide dismutase mRNA expression following ultraviolet irradiation on mouse skin.

Choung BY, **Byun SJ**, **Suh JG**, **Kim TY**.

Laboratory of Dermatology-Immunology, Catholic Research Institute of Medical Science, College of Medicine, The Catholic University of Korea, Seoul, South Korea.

Superoxide dismutases (SODs) are believed to play a crucial role in protecting cells against oxygen toxicity. There are three forms of SOD: cytosolic Cu-Zn SOD, mitochondrial Mn SOD, and extracellular SOD (EC SOD). Extracellular SOD is primarily a tissue enzyme, but the role of EC SOD in skin is unclear. Therefore, this study investigated the distribution of EC SOD in the skin using immunohistochemistry and examining the patterns of EC SOD gene expression following ultraviolet (UV) irradiation in comparison with those of Cu-Zn SOD and Mn SOD in mouse dorsal skin using Northern blot analysis. Immunohistochemical analysis showed that EC SOD was abundantly located in the epidermis as well as in the dermis, but the gene expression of EC SOD mRNA was more abundant in the dermis than in the epidermis. The gene expression levels of all three types of SODs after UV irradiation were induced differently according to the type and UV irradiation dose. The EC SOD mRNA expression level was increased relatively later than that of Cu-Zn SOD and Mn SOD. The EC SOD mRNA level was significantly higher at 6 h and 48 h after UVA irradiation and psoralen plus ultraviolet-A treatment, respectively. Ultraviolet-B irradiation increased the EC SOD mRNA expression level, with maximum at 48 h. These suggest that EC SOD participates in the majority of antioxidant systems in the skin, and it may have different defensive roles from Cu-Zn SOD and Mn SOD against UV-induced injury of the skin.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 15500641 [PubMed - indexed for MEDLINE]