J Pharm Pharmacol. 2008 Oct;60(10):1365-74.

Astaxanthin, a dietary carotenoid, protects retinal cells against oxidative stress in-vitro and in mice in-vivo. **Nakajima Y, Inokuchi Y, Shimazawa M, Otsubo K, Ishibashi T, Hara H.** Department of Biofunctional Evaluation, Molecular Pharmacology, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan. We have investigated whether astaxanthin exerted neuroprotective effects in retinal ganglion cells in-vitro and in-vivo. In-vitro, retinal damage was induced by 24-h hydrogen peroxide (H2O2) exposure or serum deprivation, and cell viability was measured using a WST assay. In cultured retinal ganglion cells (RGC-5, a rat ganglion cell-line transformed using E1A virus), astaxanthin inhibited the neurotoxicity induced by H2O2 or serum deprivation, and reduced the intracellular oxidation induced by various reactive oxygen species (ROS). Furthermore, astaxanthin decreased the radical generation induced by serum deprivation in RGC-5. In mice in-vivo, astaxanthin (100 mg kg(-1), p.o., four times) reduced the retinal damage (a decrease in retinal ganglion cells and in thickness of inner plexiform layer) induced by intravitreal N-methyl-D-aspartate (NMDA) injection. Furthermore, astaxanthin reduced the expressions of 4-hydroxy-2-nonenal (4-HNE)-modified protein (indicator of lipid peroxidation) and 8-hydroxy-deoxyguanosine (8-OHdG; indicator of oxidative DNA damage). These findings indicated that astaxanthin had neuroprotective effects against retinal damage in-vitro and in-vivo, and that its protective effects may have been partly mediated via its antioxidant effects. PMID: 18812030 [PubMed - indexed for MEDLINE]

Eye Health106

Invest Ophthalmol Vis Sci. 2008 Apr;49(4):1679-85.

Inhibition of choroidal neovascularization with an anti-inflammatory carotenoid astaxanthin. **Izumi-Nagai K, Nagai N, Ohgami K, Satofuka S, Ozawa Y, Tsubota K, Ohno S, Oike Y, Ishida S.** Laboratory of Retinal Cell Biology, Keio University of Medicne, Tokyo, Japan.

PURPOSE: Astaxanthin (AST) is a carotenoid found in marine animals and vegetables. The purpose of the present study was to investigate the effect of AST on the development of experimental choroidal neovascularization (CNV) with underlying cellular and molecular mechanisms. METHODS: Laser photocoagulation was used to induce CNV in C57BL/6J mice. Mice were pretreated with intraperitoneal injections of AST daily for 3 days before photocoagulation, and treatments were continued daily until the end of the study. CNV response was analyzed by volumetric measurements 1 week after laser injury. Retinal pigment epithelium-choroid levels of IkappaB-alpha, intercellular adhesion molecule (ICAM)-1, monocyte chemotactic protein (MCP)-1, interleukin (IL)-6, vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR)-1, and VEGFR-2 were examined by Western blotting or ELISA. AST was applied to capillary endothelial (b-End3) cells, macrophages, and RPE cells to analyze the activation of NF-kappaB and the expression of inflammatory molecules. RESULTS: The index of CNV volume was significantly suppressed by treatment with AST compared with that in vehicle-treated animals. AST treatment led to significant inhibition of macrophage infiltration into CNV and of the in vivo and in vitro expression of inflammation-related molecules, including VEGF, IL-6, ICAM-1, MCP-1, VEGFR-1, and VEGFR-2. Importantly, AST suppressed the activation of the NF-kappaB pathway, including IkappaB-alpha degradation and p65 nuclear translocation. CONCLUSIONS: AST treatment, together with inflammatory processes including NF-kappaB activation, subsequent upregulation of inflammatory molecules, and macrophage infiltration, led to significant suppression of CNV development. The present study suggests the possibility of AST supplementation as a therapeutic strategy to suppress CNV associated with AMD. Publication Types:

PMID: 18385091 [PubMed - indexed for MEDLINE]

Eye Health107

Nippon Ganka Gakkai Zasshi. 2009 Mar;113(3):403-22; discussion 423.

[Lifestyle-related diseases and anti-aging ophthalmology: suppression of retinal and choroidal pathologies by inhibiting renin-angiotensin system and inflammation] [Article in Japanese]

Ishida S. Inaida Endowed Department of Anti-Aging Ophthalmology, Laboratory of Retinal Cell Biology, Center for Integrated Medical Research, Keio University School of Medicine, Tokyo, Japan. ishidasu@sc.itc.keio.ac.jp

Lifestyle-related diseases cause macro-and microangiopathies in the major organs including the brain, heart, kidney, and eye, and as a result, shorten the lifespan. The renin-angiotensin system (RAS) has recently been shown to contribute to the processes of accelerated aging caused by lifestyle-related diseases from visceral obesity in the early stage to late-onset organ damage. Vision-threatening diabetic retinopathy and age-related macular degeneration (AMD), associated with lifestyle-related diseases as risk factors for progression, develop retinal and choroidal neovascularization (CNV), respectively, in their advanced stages. We have found that tissue RAS is activated in the pathogenesis of diabetic retinopathy and CNV, leading to angiotensin type 1 receptor(AT1-R)-mediated expression of inflammation-related molecules including vascular endothelial growth factor (VEGF), intercellular adhesion molecule (ICAM)-1, and monocyte chemotactic protein(MCP)-1. Neuronal dysfunction in diabetic retinopathy is also shown to result from AT1-R-mediated degradation of synaptic proteins. Moreover, we revealed for the first time that the receptor for prorenin [(pro) renin receptor] is expressed in the eye, although prorenin was until recently believed to be just an inactive precursor of renin. Prorenin binds to the receptor that causes dual activation of its intracellular signaling and tissue RAS, and this pathogenic mechanism is termed receptor-associated prorenin system (RAPS)'. We have demonstrated the contribution of RAPS to the pathogenesis of CNV and dual regulation of VEGF and MCP-1 by signal transduction via (pro) renin receptor and AT1-R. Next, we report the potential validity of food factor supplements as a therapeutic strategy for preventing the retinal and choroidal pathologies driven by RAS-induced inflammatory and angiogenic molecules. Functional food factors examined include lutein in yellow-green vegetables, the omega-3 polyunsaturated fatty acid eicosapentaenoic acid purified from fish oil, and red pigment astaxanthin from salmon and shrimp. We recently revealed that these food factors prevent intraocular angiogenesis and inflammation by inhibiting the expression of inflammatory molecules including VEGF, ICAM-1, and MCP-1. Preventive medicine for AMD and diabetic retinopathy, both of which have lifestyle-related diseases as a systemic background, has attracted growing attention. In the present review, we provide biological evidence for RAS inhibition and food factor supplementation in the early intervention for retinal and choroidal pathologies as an 'anti-aging ophthalmology' approach.

Eye Health108

Chem Res Toxicol. 2009 Feb 4. [Epub ahead of print]

Astaxanthin Interacts with Selenite and Attenuates Selenite-Induced Cataractogenesis. **Liao JH**, **Chen CS**, **Maher TJ**, **Liu CY**, **Lin MH**, **Wu TH**, **Wu SH**. Institute of Biological Chemistry, Academia Sinica, Taipei 115, Taiwan, Department of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts 02115, USA, and School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan. Selenite, the most commonly encountered toxic form of selenium, in overdose, is used to induce cataracts in rats. This study demonstrated that selenite, but not selenate, would interact with the carotenoid astaxanthin (ASTX), as determined using isothermal titration calorimetry and NMR. The maximum absorption of ASTX decreased with increasing selenite concentration, indicating that the conjugated system of ASTX was changed by selenite. Such interactions between ASTX and selenite were also supported by the attenuation of selenite-induced turbidity by ASTX (0-12.5 muM) in vitro. In vivo experiments also showed that ASTX attenuated selenite-induced cataractogenesis in rats. In summary, this is the first report of a direct interaction of ASTX with selenite. This interaction is supported by an in vitro assay and may be partially responsible for the ASTX observed in vivo protection against selenite-induced cataractogenesis. PMID: 19193053 [PubMed - as supplied by publisher]

Eye Health109

Ophthalmology. 2008 Feb;115(2):324-333.e2. Epub 2007 Aug 22.
Carotenoids and antioxidants in age-related maculopathy italian study: multifocal electroretinogram modifications after 1 year. Parisi V, Tedeschi M, Gallinaro G, Varano M, Saviano S, Piermarocchi S; CARMIS Study Group. Fondazione G. B. Bietti-Istituto di Ricovero e Cura a Carattere Scientifico, Roma, Italy. vparisi@tin.it OBJECTIVE: To evaluate the influence of short-term carotenoid and antioxidant supplementation on retinal function in nonadvanced age-related macular degeneration (AMD). DESIGN: Randomized controlled trial. PARTICIPANTS: Twenty-seven patients with nonadvanced AMD and visual acuity > or =0.2 logarithm of the minimum angle of resolution were enrolled and randomly divided into 2 age-similar groups: 15 patients had oral supplementation of vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), and astaxanthin (4 mg) (AZYR SIFI, Catania, Italy) daily for 12 months (treated AMD [T-AMD] group; mean age, 69.4+/-4.31 years; 15 eyes); 12 patients had no dietary supplementation during the same period (nontreated AMD [NT-AMD] group; mean age, 69.7+/-6.23 years; 12 eyes). At baseline, they were compared with 15 age-similar healthy controls. METHODS: Multifocal electroretinograms in response to 61 M-stimuli presented to the central 20 degrees of the visual field were assessed in pretreatment (baseline) conditions and, in nonadvanced AMD patients, after 6 and 12 months. MAIN OUTCOME MEASURES: Multifocal electroretinogram response amplitude densities (RAD, nanovolt/deg(2)) of the N1-P1 component of first-order binary kernels measured from 5 retinal eccentricity areas between the fovea and midperiphery: 0 degrees to 2.5 degrees (R1), 2.5 degrees to 5 degrees (R2), 5 degrees to 10 degrees (R3), 10 degrees to 15 degrees (R4), and 15 degrees to 20 degrees (R5). RESULTS: At baseline, we observed highly significant reductions of N1-P1 RADs of R1 and R2 in T-AMD and NT-AMD patients when compared with healthy controls (1-way analysis of variance $P<0.01$). N1-P1 RADs of R3-R5 observed in T-AMD and NT-AMD were not significantly different ($P>0.05$) from controls. No significant differences ($P>0.05$) were observed in N1-P1 RADs of R1-R5 between T-AMD and NT-AMD at baseline. After 6 and 12 months of treatment, T-AMD eyes showed highly significant increases in N1-P1 RADs of R1 and R2 ($P<0.01$), whereas no significant ($P>0.05$) change was observed in N1-P1 RADs of R3-R5. No significant ($P>0.05$) changes were found in N1-P1 RADs of R1-R5 in NT-AMD eyes. CONCLUSIONS: In nonadvanced AMD eyes, a selective dysfunction in the central retina (0 degrees -5 degrees) can be improved by the supplementation with carotenoids and antioxidants. No functional changes are present in the more peripheral (5 degrees -20 degrees) retinal areas. PMID: 17716735 [PubMed - indexed for MEDLINE]
Eye Health110

Exp Eye Res. 2006 Feb;82(2):275-81. Epub 2005 Aug 26.

Suppressive effects of astaxanthin against rat endotoxin-induced uveitis by inhibiting the NF-kappaB signaling pathway. **Suzuki Y, Ohgami K, Shiratori K, Jin XH, Ilieva I, Koyama Y, Yazawa K, Yoshida K, Kase S, Ohno S.** Department of Ophthalmology and Visual Sciences, Hokkaido University Graduate School of Medicine, N15 W7, Sapporo 060-8638, Japan. We investigated the effects of astaxanthin (AST), a carotenoid, on endotoxin-induced uveitis (EIU), and over the course of the disease measured the expression of inflammatory cytokines and chemokines in the presence or absence of AST. EIU was induced in male Lewis rats by footpad injection of lipopolysaccharide (LPS). The animals were randomly divided to 12 groups with eight animals in each. Immediately after the inoculation, AST (1, 10, or 100 mg kg(-1)) was injected intravenously. Aqueous humour was collected at 6, 12 and 24 hr after LPS inoculation and the number of infiltrating cells in the anterior chamber was counted. In addition, we assayed the concentration of protein, nitric oxide (NO), tumour necrosis factor-alpha (TNF-alpha) and prostaglandin E2 (PGE2). Immunohistochemical staining with a monoclonal antibody against activated NF-kappaB was performed in order to evaluate the effects of AST on NF-kappaB activation. Rats injected with AST showed a significant decrease in the number of infiltrating cells in the anterior chamber and additionally there was a significantly lower concentration of protein, NO, TNF-alpha and PGE2 in the aqueous humour. Moreover, even early stages of EIU were suppressed by injection of AST. The number of activated NF-kappaB-positive cells was lower in iris-ciliary bodies treated with 10 or 100 mg kg(-1) AST at 3 hr after LPS injection. These results suggest that AST reduces ocular inflammation in eyes with EIU by downregulating proinflammatory factors and by inhibiting the NF-kappaB-dependent signaling pathway. Publication Types:
PMID: 16126197 [PubMed - indexed for MEDLINE]
Eye Health113

Cataract formation in Atlantic salmon, Salmo salar L., smolt relative to dietary pro- and antioxidants and lipid level. **Waagbø R**, **Hamre K**, **Bjerkås E**, **Berge R**, **Wathne E**, **Lie O**, **Torstensen B**. National Institute of Nutrition and Seafood Research, Bergen, Norway. rune.waagbo@nutr.fiskeridir.no The development of cataracts in Atlantic salmon, Salmo salar L., was studied in 16 groups of smolts fed diets differing in prooxidant (iron, copper, manganese) and antioxidant (vitamin E, vitamin C, astaxanthin) composition and lipid level for 23 weeks in sea water, using a 2(7-3) reduced factorial design. The seven dietary variables were systematically varied at low (requirement level and 150 g lipid kg(-1)) and high levels (below known toxic levels and 320 g lipid kg(-1)). A mean endpoint cataract incidence of approximately 36% was observed. High dietary levels of vitamin C and astaxanthin reduced cataract frequency, whereas high dietary lipid level, iron and manganese were associated with increased cataract frequencies. Considering the nutritional status of selected organs of the fish, only the status of ascorbic acid correlated negatively to cataract development ($P < 0.05$). The lens glutathione (GSH) status was not correlated to cataract frequency, nor statistically explained by the dietary variables. However, the study shows that balancing the diet with respect to pro- and antioxidant nutrients may significantly protect Atlantic salmon against development of cataracts. An incidence of reversible osmotic cataract observed at week 14 was positively correlated to plasma glucose concentration. Publication Types:
PMID: 12962230 [PubMed - indexed for MEDLINE]
Eye Health115

Bechettobyo ni kansuru Chosa Kenkyu Heisei 14 Nendo Sokatsu, Buntan Kenkyu Hokokusho
VOL.;NO.;PAGE.98-99(2003)

Research on the anti-inflammatory effect of astaxanthin

ONO SHIGEAKI; OGAMI KAZUHIRO; SHIRATORI KENJI; ILIEVA I; KOTAKE SATOSHI; NISHIDA TOMOMI; MIZUKI NOBUHISA

The effect of astaxanthin (AST) was examined in rat model of the endotoxin induced uveitis. As the result, the protein concentration in the hydatoid lowered obviously in the group which administered 10 (AST10) or 100mg/kg (AST100) of AST in comparison with control animals.The number of inflammatory cells was significantly decreased only in AST100 group. The effect of AST on protein concentration and cell numbers in the hydatoid in AST100 group was almost equivalent to those of 10mg/kg of prednisolone (PSL) administrated group. Any side effects by AST administration could not be observed. AST showed dose-dependent inhibitory effect in this model. Therefore, it was indicated that AST could be utilized as a new antiphlogistic for ophthalmia disease.

Eye Health119

Atarashii Ganka, 25(10):1461-1464 (In Japanese). 2008

Intraocular penetration of astaxanthin in rabbit eyes

Fukuda et al.,

In a new study, natural astaxanthin extract derived from Haematococcus microalgae was detected in the iris/ciliary body of New Zealand Albino (NZW) Rabbit Eyes 24 hours after ingestion. Astaxanthin has been reported to have many benefits in the eye. Several human clinical studies reported the alleviation of eye fatigue (by improving accommodation function) in visual display terminal (VDT) workers after oral supplementation. However, up to now there has been no intraocular kinetic information available. In collaboration between the Ophthalmology Department of Kanazawa Medical University, Japan, and Fuji Chemical Industry, Japan, researchers investigated the ocular and blood serum levels of astaxanthin in 24 NZW albino rabbits. After administering a 100 mg/kg single oral dose, astaxanthin was determined by careful extraction followed by HPLC analysis over a period of 168 hours. According to the astaxanthin detection system, the time taken to reach maximum presence (Tmax) in serum and iris/ciliary body was 9 hours (at Cmax 61.3 ng/mL) and 24 hours (at Cmax 79.3) respectively. In other human studies with oral intake of astaxanthin, the Tmax in serum ranged between 9 and 12 hours.

The intraocular penetration kinetics could have a similar pattern to humans but further study is necessary. This study adds to the growing body of science supporting astaxanthin's benefits for eye fatigue caused by VDT use.

Eye Health120

Invest Ophthalmol Vis Sci. 2003 Jun;44(6):2694-701

Effects of astaxanthin on lipopolysaccharide-induced inflammation in vitro and in vivo

Ohgami K, Shiratori K, Kotake S, Nishida T, Mizuki N, Yazawa K, Ohno S
Department of Ophthalmology and Visual Sciences, Hokkaido University Graduate School of Medicine, Sapporo, Japan. kohgami@med.hokudai.ac.jp

PURPOSE: Astaxanthin (AST) is a carotenoid that is found in marine animals and vegetables. Several previous studies have demonstrated that AST exhibits a wide variety of biological activities including antioxidant, antitumor, and anti-Helicobacter pylori effects. In this study, attention was focused on the antioxidant effect of AST. The object of the present study was to investigate the efficacy of AST in endotoxin-induced uveitis (EIU) in rats. In addition, the effect of AST on endotoxin-induced nitric oxide (NO), prostaglandin E2 (PGE2), and tumor necrosis factor (TNF)-alpha production in a mouse macrophage cell line (RAW 264.7) was studied in vitro. METHODS: EIU was induced in male Lewis rats by a footpad injection of lipopolysaccharide (LPS). AST or prednisolone was administered intravenously at 30 minutes before, at the same time as, or at 30 minutes after LPS treatment. The number of infiltrating cells and protein concentration in the aqueous humor collected at 24 hours after LPS treatment was determined. RAW 264.7 cells were pretreated with various concentrations of AST for 24 hours and subsequently stimulated with 10 microg/mL of LPS for 24 hours. The levels of PGE2, TNF-alpha, and NO production were determined in vivo and in vitro. RESULTS: AST suppressed the development of EIU in a dose-dependent fashion. The anti-inflammatory effect of 100 mg/kg AST was as strong as that of 10 mg/kg prednisolone. AST also decreased production of NO, activity of inducible nitric oxide synthase (NOS), and production of PGE2 and TNF-alpha in RAW264.7 cells in vitro in a dose-dependent manner. CONCLUSIONS: This study suggests that AST has a dose-dependent ocular anti-inflammatory effect, by the suppression of NO, PGE2, and TNF-alpha production, through directly blocking NOS enzyme activity.

Eye Health124

Regul Toxicol Pharmacol. 2010 Oct;58(1):121-30. Epub 2010 May 8.

Suppressive effect of astaxanthin on retinal injury induced by elevated intraocular pressure. Cort A, Ozturk N, Akpinar D, Unal M, Yucel G, Ciftcioglu A, Yargicoglu P, Aslan M.
Department of Biochemistry, Akdeniz University, School of Medicine, Antalya 07070, Turkey.

Abstract

The aim of this study was to clarify the possible protective effect of astaxanthin (ASX) on the retina in rats with elevated intraocular pressure (EIOP). Rats were randomly divided into two groups which received olive oil or 5mg/kg/day ASX for a period of 8 weeks. Elevated intraocular pressure was induced by unilaterally cauterizing three episcleral vessels and the unoperated eye served as control. At the end of the experimental period, neuroprotective effect of ASX was determined via electrophysiological measurements of visual evoked potentials (VEP) and rats were subsequently sacrificed to obtain enucleated globes which were divided into four groups including control, ASX treated, EIOP, EIOP+ASX treated. Retinoprotective properties of ASX were determined by evaluating retinal apoptosis, protein carbonyl levels and nitric oxide synthase-2 (NOS-2) expression. Latencies of all VEP components were significantly prolonged in EIOP and returned to control levels following ASX administration. When compared to controls, EIOP significantly increased retinal protein oxidation which returned to baseline levels in ASX treated EIOP group. NOS-2 expression determined by Western blot analysis and immunohistochemical staining was significantly greater in rats with EIOP compared to ASX and control groups. Retinal TUNEL staining showed apoptosis in all EIOP groups; however ASX treatment significantly decreased the percent of apoptotic cells when compared to non treated ocular hypertensive controls. The presented data confirm the role of oxidative injury in EIOP and highlight the protective effect of ASX in ocular hypertension.
Eye Health 127

J Pharm Pharmacol. 2008 Oct;60(10):1365-74.

Astaxanthin, a dietary carotenoid, protects retinal cells against oxidative stress in-vitro and in mice in-vivo.

Nakajima Y, Inokuchi Y, Shimazawa M, Otsubo K, Ishibashi T, Hara H.

Source

Department of Biofunctional Evaluation, Molecular Pharmacology, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan.

Abstract

We have investigated whether astaxanthin exerted neuroprotective effects in retinal ganglion cells in-vitro and in-vivo. In-vitro, retinal damage was induced by 24-h hydrogen peroxide (H2O2) exposure or serum deprivation, and cell viability was measured using a WST assay. In cultured retinal ganglion cells (RGC-5, a rat ganglion cell-line transformed using E1A virus), astaxanthin inhibited the neurotoxicity induced by H2O2 or serum deprivation, and reduced the intracellular oxidation induced by various reactive oxygen species (ROS). Furthermore, astaxanthin decreased the radical generation induced by serum deprivation in RGC-5. In mice in-vivo, astaxanthin (100 mg kg(-1), p.o., four times) reduced the retinal damage (a decrease in retinal ganglion cells and in thickness of inner plexiform layer) induced by intravitreal N-methyl-D-aspartate (NMDA) injection. Furthermore, astaxanthin reduced the expressions of 4-hydroxy-2-nonenal (4-HNE)-modified protein (indicator of lipid peroxidation) and 8-hydroxy-deoxyguanosine (8-OHdG; indicator of oxidative DNA damage). These findings indicated that astaxanthin had neuroprotective effects against retinal damage in-vitro and in-vivo, and that its protective effects may have been partly mediated via its antioxidant effects.

PMID: 18812030 [PubMed - indexed for MEDLINE]

Eye Health