Glaucoma
Updated: 08/26/2004

ABSTRACTS

Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons.

Akaike A, Tamura Y, Sato Y, et al.

Eur J Pharmacol. 1993 Sep 7; 241(1):1-6.

The effects of methylcobalamin, a vitamin B12 analog, on glutamate-induced neurotoxicity were examined using cultured rat cortical neurons. Cell viability was markedly reduced by a brief exposure to glutamate followed by incubation with glutamate-free medium for 1 h. Glutamate cytotoxicity was prevented when the cultures were maintained in methylcobalamin-containing medium. Glutamate cytotoxicity was also prevented by chronic exposure to S-adenosylmethionine, which is formed in the metabolic pathway of methylcobalamin. Chronic exposure to methylcobalamin and S-adenosylmethionine also inhibited the cytotoxicity induced by N-methyl-D-aspartate or sodium nitroprusside that releases nitric oxide. In cultures maintained in a standard medium, glutamate cytotoxicity was not affected by adding methylcobalamin to the glutamate-containing medium. In contrast, acute exposure to MK-801, a NMDA receptor antagonist, prevented glutamate cytotoxicity. These results indicate that chronic exposure to methylcobalamin protects cortical neurons against NMDA receptor-mediated glutamate cytotoxicity

Blood levels of thiamine and ascorbic acid in chronic open-angle glaucoma.

Asregadoo ER.

Ann Ophthalmol. 1979 Jul; 11(7):1095-100.

Blood levels of thiamine and ascorbic acid in chronic open-angle glaucoma are determined in this study. Dietary vitamin intake was compared with thiamine and ascorbic acid blood levels in a sample of 38 patients with glaucoma and 12 controls. These patients had a statistically significant lower thiamine blood level than controls (P less than 0.001), but no significant difference was found for ascorbic acid blood levels. Poor absorption of thiamine occurred in the glaucomatous patients in this study

Pathophysiology of pigment dispersion syndrome and pigmentary glaucoma.

Campbell DG, Schertzer RM.

Curr Opin Ophthalmol. 1995 Apr; 6(2):96-101.

Pigmentary glaucoma results from zonular-pigment dispersion, primarily in young, myopic, white individuals. The concavity of the midperipheral iris allows iridozonular contact. Released pigment is carried to the trabecular meshwork where it resides: (1) benignly, not affecting the intraocular pressure, as in pigment dispersion syndrome; or (2) malignantly, elevating the intraocular pressure, as in pigmentary glaucoma. Small amounts of pigment are quickly phagocytized. If the particulate load is heavy, the cells migrate further along the outflow pathway. The flattening of the iris in pigmentary glaucoma patients receiving iridotomies, along with the backward flow of pigment observed during treatment, demonstrates a greater pressure in the anterior than the posterior chamber. This reverse pupillary block may be due to temporary ocular deformations caused by blinking, as small aqueous aliquots are forced into the anterior chamber. Flattening of the concave iris is the key to current and future management of these patients

Latanoprost, a prostaglandin analog, for glaucoma therapy. Efficacy and safety after 1 year of treatment in 198 patients. Latanoprost Study Groups.

Camras CB, Alm A, Watson P, et al.

Ophthalmology. 1996 Nov; 103(11):1916-24.

PURPOSE: To determine efficacy and safety of latanoprost, a prostaglandin analog for glaucoma, during 1 year of treatment. METHODS: After baseline measurements, 0.005% latanoprost was topically applied once daily for 12 months in patients from Scandinavia, the United Kingdom, and the United States who had elevated intraocular pressure (IOP). Diagnoses included ocular hypertension, chronic open-angle glaucoma, exfoliation syndrome, and pigment dispersion syndrome. Treatment was masked for the first 6 months and open-label during the second 6 months. RESULTS: Of the 272 patients initially enrolled, withdrawals were due to inadequate IOP control (1%), increased iris pigmentation (5%), other ocular problems (3%), systemic medical problems (3%), and nonmedical reasons (14%). Latanoprost significantly ($P < 0.0001$) reduced diumal IOP from 25.3 +/- 3.0 mmHg (mean +/- standard deviation) at baseline to 17.4 +/- 2.7 mmHg (32% reduction) at 12 months in the 198 patients who completed 1 year of treatment. The IOP reduction was maintained at a consistent level throughout the 12 months without evidence of drift, and was not affected by sex, age, race, or eye color. Overall, latanoprost caused a possible or definite increase in iris pigmentation in 12% of the 272 patients, all of whom had multicolored irides at baseline. One half of these patients with increased pigmentation withdrew before completing 1 year of therapy. Visual field, optic disc cupping, visual acuity, refractive error, conjunctival hyperemia, aqueous flare, anterior chamber cellular response, lens examination, blood pressure, heart rate, blood tests, and urinalysis were not appreciably altered. CONCLUSION: Latanoprost safely and effectively reduces IOP for 1 year in patients of diverse nationalities, providing further evidence for its usefulness in chronic glaucoma therapy

Forskolin lowers intraocular pressure by reducing aqueous inflow.

Caprioli J, Sears M, Bausher L, et al.

Invest Ophthalmol Vis Sci. 1984 Mar; 25(3):268-77.

Forskolin is a diterpene derivative of the plant Coleus forskohlii that stimulates adenylate cyclase activity without interacting with cell surface receptors. Forskolin lowers the intraocular pressure of rabbits, monkeys, and humans. In rabbits, net aqueous humor inflow decreases, outflow facility remains unchanged, and ciliary blood flow increases. Tolerance to the intraocular pressure lowering effect did not occur in rabbits after topical doses given every 6 hr for 15 days. In vitro forskolin activates adenylate cyclase of crude particulate homogenates prepared from cultured human ciliary epithelia or from dissected ciliary epithelial processes of rabbit or human eyes. This activation is not blocked by timolol. The stimulation of adenylate cyclase by isoproterenol in vitro is potentiated in the presence of forskolin. Forskolin represents a potentially useful class of antiglaucoma agents differing in molecular mechanism of action from previously used drugs

The Green Pharmacy.

Duke JA.

1997;

[Lipoic acid as a means of metabolic therapy of open-angle glaucoma].

Filina AA, Davydova NG, Endrikhovskii SN, et al.

Vestn Oftalmol. 1995 Oct; 111(4):6-8.

A total of 45 patients (90 eyes) with stages I and II open-angle glaucoma (OAG) were examined, 26 of these were administered lipoic acid in a daily dose of 0.075 g for 2 months and 19 were given 0.15 g daily for 1 month. Control group consisted of 31 patients with OAG who were administered only local hypotensive therapy. Vision acuity and visual field were checked up, tonometry, tonography, and campimetry carried out, and levels of nonprotein SH-groups and activity of gamma-glutamyl transpeptidase measured in the lacrimal fluid. Improvement of the biochemical parameters, visual function, and of the coefficient of efficacy of liquid discharge was more expressed in the patients administered lipoic acid in a daily dose of 0.15 g. Color campimetry results indicate improved sensitivity of the visual analyzer under the effect of treatment. Improvement was attained in approximately 45-47.5% of examined eyes, and was more often seen in patients with stage II OAG: in 57-58% eyes. The effect of lipoic acid may be explained by its antioxidant properties and direct influence on ocular tissue metabolism

Vascular dysregulation: a principal risk factor for glaucomatous damage?

Flammer J, Haefliger IO, Orgul S, et al.

J Glaucoma. 1999 Jun; 8(3):212-9.

Both intraocular pressure (IOP) and vascular factors appear to play an important role in the pathogenesis of glaucomatous optic neuropathy (GON). Arteriosclerosis and its risk factors are of minor importance, whereas vasospastic syndrome clearly is

associated with GON. A vascular endotheliopathy seems to be involved in the diathetic hyperresponsiveness to stimuli, such as coldness or emotional stress. This in turn leads to a compromised autoregulation, and thereby renders the eye more sensitive to IOP or to a decrease in blood pressure. A variation in ocular perfusion may lead to an increase in free oxygen radicals. This may finally lead to apoptosis

HP 663: a novel compound for the treatment of glaucoma.

Hartman HBRJEKBLKRWJrCRJPWWCPG.

Drug Dev Res. 1988; 12(3-4):197-209.

Natural therapies for ocular disorders, part two: cataracts and glaucoma.

Head KA.

Altern Med Rev. 2001 Apr; 6(2):141-66.

Pathophysiological mechanisms of cataract formation include deficient glutathione levels contributing to a faulty antioxidant defense system within the lens of the eye. Nutrients to increase glutathione levels and activity include lipoic acid, vitamins E and C, and selenium. Cataract patients also tend to be deficient in vitamin A and the carotenes, lutein and zeaxanthin. The B vitamin riboflavin appears to play an essential role as a precursor to flavin adenine dinucleotide (FAD), a co-factor for glutathione reductase activity. Other nutrients and botanicals, which may benefit cataract patients or help prevent cataracts, include pantethine, folic acid, melatonin, and bilberry. Diabetic cataracts are caused by an elevation of polyols within the lens of the eye catalyzed by the enzyme aldose reductase. Flavonoids, particularly quercetin and its derivatives, are potent inhibitors of aldose reductase. Glaucoma is characterized by increased intraocular pressure (IOP) in some but not all cases. Some patients with glaucoma have normal IOP but poor circulation, resulting in damage to the optic nerve. Faulty glycosaminoglycan (GAG) synthesis or breakdown in the trabecular meshwork associated with aqueous outflow has also been implicated. Similar to patients with cataracts, those with glaucoma typically have compromised antioxidant defense systems as well. Nutrients that can impact GAGs such as vitamin C and glucosamine sulfate may hold promise for glaucoma treatment. Vitamin C in high doses has been found to lower IOP via its osmotic effect. Other nutrients holding some potential benefit for glaucoma include lipoic acid, vitamin B12, magnesium, and melatonin. Botanicals may offer some therapeutic potential. Ginkgo biloba increases circulation to the optic nerve; forskolin (an extract from Coleus forskohlii) has been used successfully as a topical agent to lower IOP; and intramuscular injections of Salvia miltiorrhiza have shown benefit in improving visual acuity and peripheral vision in people with glaucoma

Stress reactivity of intraocular pressure after relaxation training in open-angle glaucoma patients.

Kaluza G, Strempel I, Maurer H.

J Behav Med. 1996 Dec; 19(6):587-98.

The present study was based on the hypothesis that stress may contribute to increased intraocular pressure (IOP) in open-angle glaucoma patients. It is investigated whether IOP reactivity to a mental stressor test (MST) can be influenced by relaxation training. Twenty three patients with open-angle glaucoma were randomly assigned either to a training group (TG) or to a waiting-list control group (CG). Prior to as well as after the completion of the training all patients were exposed to the MST. IOP and heart rate as well as self-ratings of psychological strain were assessed three times: (1) at baseline, (2) after exposition to the stressor, and (3) after a 10-min relaxation phase. Results provide evidence that the MST is a valid procedure to induce psychophysiological activation and that elevated IOP levels in open-angle glaucoma patients might be provoked by stressing situations. However, participation in the relaxation training did not influence IOP stress reactivity

Protective effects of methylcobalamin, a vitamin B12 analog, against glutamate-induced neurotoxicity in retinal cell culture.

Kikuchi M, Kashii S, Honda Y, et al.

Invest Ophthalmol Vis Sci. 1997 Apr; 38(5):848-54.

PURPOSE: To examine the effects of methylcobalamin on glutamate-induced neurotoxicity in the cultured retinal neurons. METHODS: Primary cultures obtained from the fetal rat retina (gestation days 16 to 19) were used for the experiment. The neurotoxicity was assessed quantitatively using the trypan blue exclusion method. RESULTS: Glutamate neurotoxicity was prevented by chronic exposure to methylcobalamin and S-adenosylmethionine (SAM), which is formed in the metabolic pathway of methylcobalamin. Chronic exposure to methylcobalamin and SAM also inhibited the neurotoxicity induced by sodium

nitroprusside that release nitric oxide. By contrast, acute exposure to methylcobalamin did not protect retinal neurons against glutamate neurotoxicity. CONCLUSIONS: Chronic administration of methylcobalamin protects cultured retinal neurons against N-methyl-D-aspartate-receptor-mediated glutamate neurotoxicity, probably by altering the membrane properties through SAM-mediated methylation

Cyclooxygenase and lipoxygenase pathways in anterior uvea and conjunctiva.

Kulkarni PS, Srinivasan BD.

Prog Clin Biol Res. 1989; 312:39-52.

It has been demonstrated that normal, uninflamed, anterior uvea and conjunctiva of different species have the capacity to synthesize cyclooxygenase and lipoxygenase products. Cyclooxygenase activity is greater than lipoxygenase activity in both anterior uvea and conjunctival tissues. Other ocular tissues such as cornea, lens, and retina were found to have much lesser capacity than the conjunctiva and anterior uvea to synthesize cyclooxygenase and lipoxygenase products from arachidonic acid. In our preliminary studies, we also observed that human retina have considerably less ability to metabolize AA into cyclooxygenase and lipoxygenase activity. The finding that the anterior uvea of all species studied has a high capacity to synthesize PGs and other cyclooxygenase products maybe of particular physiological significance since several investigators have demonstrated that PGE2 and PGF2 alpha in low doses, lower intraocular pressure in all species studied, including the human eye. Additionally, PGE2 can be shown to have some anti-inflammatory effects. In light of these observations, we must consider that the high endogenous cyclooxygenase activity in normal conjunctiva and anterior uvea may play a role in maintaining normal intraocular pressure and in preventing the development of inflammation in response to normal environmental stimuli. Arachidonic acid is also metabolized into biologically active compounds by cytochrome P450 in corneal endothelium. It is not yet known whether or not other ocular tissues also have the ability to metabolize arachidonic acid via this pathway and whether these compounds, when synthesized from endogenous arachidonic acid stores in vivo have any biological effects on the eye. Studies on omega-3 fatty acid metabolism were done for two main reasons: (1) PGE3 and PGD3 lowered intraocular pressure without causing ocular inflammation in rabbit; and (2) some surveys demonstrated that in Greenland Eskimos whose marine diet is enriched with omega-3 substrate eicosapentaenoic acid, have a lower incidence of open-angle glaucoma as compared to Caucasians, whose diet is rich in arachidonic acid. The ability of anterior uvea to synthesize PGE3 and PGD3 in human, monkey, and rabbit anterior uvea warrants further investigation to determine whether or not these omega-3 PGs play a role in lowering intraocular pressure

Complementary Medicine: An Integrated Approach.

Lewith G.

1996;108-9.

[The antioxidant activity of the lacrimal fluid in patients with primary open-angle glaucoma].

Makashova NV, Babenkova IV, Teselkin I.

Vestn Oftalmol. 1999 Sep; 115(5):3-4.

Antioxidant activity (AOA) of lacrimal fluid and blood plasma was studied in 10 normal subjects (20 eyes) and 35 patients with primary open-angle glaucoma (POAG) (67 eyes with glaucoma at different stages). The findings indicate that the progress of glaucoma is paralleled by a gradual decrease in the lacrimal fluid AOA, which becomes significant at the third stage of POAG. Plasma AOA also decreased significantly in the third far advanced stage. A course of total antioxidant therapy including oral aevit and vitamin complexes and intramuscular ascorbic acid normalized plasma AOA even in patients with far advanced glaucoma, while the lacrimal AOA did not normalize. Therefore, local antioxidants are preferable in glaucoma patients

The effectiveness of dapiprazole in preventing exercise-induced IOP increase in patients with pigmentary dispersion syndrome.

Mastropasqua L, Carpineto P, Ciancaglini M, et al.

Int Ophthalmol. 1995; 19(6):359-62.

PURPOSE: The authors investigated the use of dapiprazole, an alpha-adrenergic blocking agent, in preventing pigment release and IOP increase after exercise in patients affected with PDS. METHODS: Three young myopic males (31, 34 and 35 years old) affected with pigmentary dispersion syndrome performed 30 minutes of jogging on a computerized treadmill. Telemetric heartbeat measurement was performed to obtain constant pulse rate training. Computerized tonography and IOP measurement

were performed 10 minutes after the exercise. After one month the patients repeated the same exercise after pre-treatment with dapiprazole 0.5% eyedrops (one drop 30, 20 and 10 minutes before the exercise). Ten minutes after the exercise IOP measurements and computerized tonography were repeated. RESULTS: After 30 minutes of exercise IOP measurements showed values ranging from 19 to 45 mmHg (mean 30.33; SD 8.73). Computerized tonography C values after exercise ranged from 0.04 to 0.16 (mean 0.09; SD 0.04). After pre-treatment with dapiprazole 0.5% eyedrops, IOP values ranged from 18 to 28 mmHg (mean 23.33; SD 3.44) and tonography C values ranged from 0.10 to 0.20 (mean 0.14; SD 0.03). CONCLUSIONS: The study supports the concept that exercise-induced pigment release temporarily obstructs the acqueous outflow channels, causing IOP increase in some patients with PDS. Pre-treatment with dapiprazole was useful in reducing IOP spikes and in increasing tonographic total outflow facility after exercise. The absence of induced myopia and the lack of dangerous vitreoretinal tractions on retinal periphery make dapiprazole a safe method to reduce exercise-induced pigment dispersion

Nitric oxide mediates excitotoxic and anoxic damage in rat retinal ganglion cells cocultured with astroglia.

Morgan J, Caprioli J, Koseki Y.

Arch Ophthalmol. 1999 Nov; 117(11):1524-9.

BACKGROUND: Nitric oxide has been implicated in the process of retinal ganglion cell death in glaucoma. OBJECTIVE: To investigate the role of nitric oxide in mediating retinal ganglion cell death in a culture system that models glial-neuronal interactions at the level of the optic nerve head. METHODS: Dissociated retinal ganglion cells from neonatal rats were plated on monolayers of astroglia and identified by retrograde labeling with the fluorescent marker 1.1-dioctadecyl-,3,3,3,tetramethylindocarbocyanineperchlorate. Two days after dissociation, cocultures of retinal ganglion cells and glia were treated with graded concentrations of the nitric oxide synthase inhibitor N-nitro-L-arginine (NNA), and exposed to either anoxia for 1 to 24 hours or excitatory amino acids for 6 hours. Surviving retinal ganglion cells were counted with fluorescence microscopy and expressed as a percentage of retinal ganglion cells surviving in control cultures. RESULTS: Cell survival after anoxia increased in a dose-dependent fashion with exposure to NNA. Mean +/- SD survival rate of retinal ganglion cells after 6 hours of anoxia was 57%+/-10% with NNA treatment compared with 31%+/-3% without treatment (P<.01). When treated with excitatory amino acids, cell survival was 31%+/-6% after administration of N-methyl D-aspartate, 500 micromol/L, and 27%+/-8% after administration of sodium glutamate, 500 micromol/L. Survival was increased in cultures with exposure to NNA, 100 micromol/L, to 53%+/-11% and 69%+/-11%, respectively (P<.01). CONCLUSION: In this coculture of retinal ganglion cells and astroglia, reduction of the glial source of nitric oxide through nitric oxide synthase inhibition provided partial but significant protection against the lethal effects of anoxia and excitatory amino acids on retinal ganglion cells. CLINICAL RELEVANCE: Neuroprotective agents may play a role in patients with glaucoma who have progressive visual field loss, despite satisfactory control of intraocular pressure. Inhibition of nitric oxide synthase at the level of the optic nerve head may contribute to a clinically significant level of neuroprotection

Excitotoxins in foods.

Olney JW.

Neurotoxicology. 1994; 15(3):535-44.

Evidence is reviewed pertaining to excitatory neurotoxins (excitotoxins) encountered in human food supply. The most frequently encountered food excitotoxin is glutamate (Glu) which is commercially added to many foods despite evidence that it can freely penetrate certain brain regions and rapidly destroy neurons by hyperactivating the NMDA subtype of Glu receptor. Hypersensitivity of NMDA receptors during development makes the immature nervous system especially sensitive to Glu excitotoxicity. On the other hand, elderly consumers are particularly sensitive to domoic acid, a powerful excitotoxic Glu analog that activates both NMDA and non-NMDA receptors. A high content of domoic acid in shell fish caused a recent food poisoning incident that killed some elderly victims and caused brain damage and memory impairment in others. Neurolathyrism is a crippling neurodegenerative condition associated with ingestion of a legume that naturally contains BOAA, an excitotoxic Glu analog that hyperactivates non-NMDA receptors. Thus, the human food supply is a source of excitotoxins that can damage the brain by one type of mechanism to which immature consumers are hypervulnerable, or by other mechanisms to which adult and elderly consumers are peculiarly sensitive

The potential of neuroprotection in glaucoma treatment.

Osborne NN, Chidlow G, Nash MS, et al.

Curr Opin Ophthalmol. 1999 Apr; 10(2):82-92.

Visual field loss in glaucoma is due to death of retinal ganglion cells. Reducing or slowing down the loss of ganglion cells in glaucoma, a concept known as neuroprotection, would appear to be the only way forward. This does not imply that treatment of

risk factors, such as elevated intraocular pressure, must not be continuously implemented. In this paper we point out that very little is known about the mechanisms of ganglion cell death in glaucoma and that data derived from studies on the "ideal animal model for glaucoma" must not be overemphasized. We also propose that the death processes of neurones in various diseases are fundamentally the same but vary in cause. Experimental data show that the death rate of neuronal populations is dependent on the impact of the insult and that neuroprotectants are more likely to benefit a patient in diseases in which the neurones die slowly, as in glaucoma, than in a disease in which the death of a set of neurones is rapid. We conclude that if a putative neuroprotectant can be administered in such a way that it reaches the retina in appropriate amounts and has insignificant side effects, it is likely to attenuate ganglion cell death and thus benefit the glaucoma patient

Neuroprotection in relation to retinal ischemia and relevance to glaucoma.

Osborne NN, Ugarte M, Chao M, et al.

Surv Ophthalmol. 1999 Jun; 43 Suppl 1:S102-S128.

Management of glaucoma is directed at the control of intraocular pressure (IOP), yet it is recognized now that increased IOP isjust an important risk factor in glaucoma. Therapy that prevents the death of ganglion cells is the main goal of treatment, but an understanding of the causes of ganglion cell death and precisely how it occurs remains speculative. Present information supports the working hypothesis that ganglion cell death may result from a particular form of ischemia. Support for this view comes from the fact that not all types of retinal ischemia lead to the pathologic findings seen in glaucomatous retinas or to cupping in the optic disk area. Moreover, in animal experiments in which ischemia is caused by elevated IOP, a retinal abnormality similar to that seen in true glaucoma is produced, whereas after occlusion of the carotid arteries a different pattern of damage is found. In ischemia, glutamate is released, and this initiates the death of neurons that contain ionotropic glutamate (NMDA) receptors. Elevated glutamate levels exist in the vitreous humor of patients with glaucoma, and NMDA receptors exist on ganglion cells and a subset of amacrine cells. Experimental studies have shown that a variety of agents can be used to prevent the death of retinal neurons (particularly ganglion cells) induced by ischemia. These agents are generally those that block NMDA receptors to prevent the action of the released glutamate or substances that interfere with the subsequent cycle of events that lead to cell death. The major causes of cell death after activation of NMDA receptors are the influx of calcium into cells and the generation of free radicals. Substances that prevent this cascade of events are, therefore, often found to act as neuroprotective agents. For a substance to have a role as a neuroprotective agent in glaucoma, it would ideally be delivered topically to the eye and used repeatedly. It is, therefore, of interest that betaxolol, a beta-blocker presently used to reduce IOP in humans, also has calcium channel-blocking functions. Moreover, experimental studies show that betaxolol is an efficient neuro protective agent against retinal ischemia in animals, when injected directly into the eye or intraperitoneally

Abnormal formation of collagen cross-links in skin fibroblasts cultured from patients with Ehlers-Danlos syndrome type VI.

Pasquali M, Still MJ, Vales T, et al.

Proc Assoc Am Physicians. 1997 Jan; 109(1):33-41.

Ehlers-Danlos syndrome type VI (EDS VI) is an autosomal recessive disorder of connective tissue characterized by hyperextensible, friable skin and joint hypermobility. Severe scoliosis and ocular fragility are present in some patients. This disease is caused by defective collagen lsyl hydroxylase, a vitamin C-dependent enzyme that converts lysyl residues to hydroxylysine on procollagen peptides. Hydroxylysine is essential for the formation of the covalent pyridinium cross-links pyridinoline (Pyr) and deoxypyridinoline (Dpyr), among mature collagen molecules. Pyr derives from three hydroxylysyl residues, whereas Dpyr derives from one lysyl and two hydroxylysyl residues. Patients with EDS VI have high urinary excretion of Dpyr, resulting in a high ratio of Dpyr-Pyr. In this study, we evaluate content and production of pyridinium cross-links in the skin and cultured fibroblasts from patients with EDS VI. The skin of normal controls contained both Pyr and Dpyr, with a marked predominance of Pyr as observed in normal urine. The skin of patients with EDS VI had reduced total content of pyridinium cross-links, with the presence of Dpyr but not Pyr. Long-term cultures of control fibroblasts produced both Pyr and Dpyr, with a pattern resembling that of normal skin. By contrast, cross-links were not detected in dermal fibroblasts cultured from patients with EDS VI. Vitamin C, which improves the clinical manifestations of some patients with EDS VI, decreased Dpyr accumulation though only minimally affecting Pyr content in control cells. By contrast, addition of vitamin C to fibroblasts from patients with EDS VI stimulated the formation of Dpyr more than that of Pyr and greatly increased total pyridinium cross-link formation. These results indicate that qualitative and quantitative alterations of pyridinium cross-links occur in skin and in cultured dermal fibroblasts of patients with EDS VI and may be responsible for their abnormal skin findings. The vitamin C-stimulated production of Dpyr and Pyr in fibroblasts from patients with EDS VI may explain at least in part the therapeutic effects of this vitamin in EDS VI

Ascorbic acid in the treatment of alkali burns of the eye.

Pfister RR, Paterson CA.

Ophthalmology. 1980 Oct; 87(10):1050-7.

Severe ocular alkali burns in rabbits result in a decrease in aqueous humor ascorbate levels to one-third normal levels. If this deficiency is reversed by immediate treatment with parenteral or topical ascorbate, there is a significantly decreased incidence of subsequent corneal ulceration and perforation. The morphologic changes in these ulcerating corneas are typical of those noted in scorbutus (scurvy). It is concluded that alkali injury to the ciliary epithelial transport processes or ciliary body vasculature results in localized deficiency of ascorbic acid in the aqueous humor and cornea. The development of corneal ulceration is thought to be based on this deficiency which results in the failure of fibroblasts to produce sufficient collagen for repair. A randomized clinical trial of ascorbic acid in the treatment of human alkali burned eyes is now underway

Optic neuropathy from thiamine deficiency in a patient with ulcerative colitis.

van Noort BA, Bos PJ, Klopping C, et al.

Doc Ophthalmol. 1987 Sep; 67(1-2):45-51.

A 35-year-old man with ulcerative colitis who was receiving parenteral feeding with large amounts of glucose, suddenly developed severe optic neuropathy and oculomotor palsy. The visual acuity fell bilaterally to 0. Although it was stated that thiamine has been regularly supplemented in the preceding period, high doses of vitamin B1 were given. Visual acuity promptly returned to 1.0 but large visual field defects persisted. Later on it appeared that erroneously no vitamin B1 has been given before

[The excitotoxicity theory of glaucoma].

Vorwerk CK, Naskar R, Dreyer EB.

Klin Monatsbl Augenheilkd. 1999 Jan; 214(1):2-11.

Glaucoma can be defined as a disease in which one of the pathophysiological consequences of raised intra-ocular pressure is damage of the optic nerve, and subsequently the loss of retinal ganglion cells (RGCs). One of the main aims of modern glaucoma therapy is to alter the intraocular pressure, either surgically or pharmacologically. Recently it was shown that the vitreous of glaucoma patients contains increased levels of glutamate (27 microM as compared to 11 microM in controls). This concentration of glutamate is sufficient to induce retinal ganglion cell death. The rise in intraocular pressure is probably the initial insult, which enhances the increase or release of glutamate. Although the increase in intravitreal glutamate levels is an accompanying feature of glaucoma, it could contribute to the loss of retinal ganglion cells in humans itself. Therefore, despite efficient control of intra-ocular pressure, RGC's loss will continue resulting in further visual impairment, if the toxic effect of glutamate is not blocked. If it would be possible to understand the mechanism leading to excessive vitreous levels of glutamate in glaucoma or to block its toxic effects, then the resulting visual loss could be retarded. This review discusses various proposed mechanisms leading to intraocular glutamate toxicity and the role of neuroprotection in this disease. (Literature search by Medline)

An experimental basis for implicating excitotoxicity in glaucomatous optic neuropathy.

Vorwerk CK, Gorla MS, Dreyer EB.

Surv Ophthalmol. 1999 Jun; 43 Suppl 1:S142-S150.

Most therapy for glaucoma is directed at the management of the intraocular pressure (IOP). Conventional wisdom holds that excessive pressure within the eye leads to the ganglion cell loss/optic nerve damage seen in this disease. Both glutamate and elevated IOP can selectively damage the retinal ganglion cells in the mammalian eye. We have identified an elevated level of glutamate in the vitreous humor of glaucoma patients (27 microM as compared to 11 microM in the control population). This concentration of glutamate suffices--on its own--to kill retinal ganglion cells. It is plausible that the IOP may represent an initial insult that precipitates the production of excessive glutamate. Therefore, even if glutamate elevation is an epiphenomenon associated with the course of the disease, it may contribute to ganglion cell loss in humans. Lowering the IOP may slow down glutamate production, but if nothing is done to block the toxic effects of glutamate as well, visual loss may result despite excellent IOP control. If interventions can be found to retard the production or toxic effects of glutamate, it may be possible to slow glaucomatous visual loss

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