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Is There More to Glaucoma Treatment Than Lowering IOP?

Maneli Mozaffarieh, MD, and Josef Flammer, MD

University Eye Clinic, Basel, Switzerland

Abstract. Classic glaucoma treatment focuses on intraocular pressure (IOP) reduction. Better knowledge of the pathogenesis of the disease has opened up new therapeutical approaches. Whereas most of these new avenues of treatment are still in the experimental phase, others, such as magnesium, gingko, salt and fludrocortisone, are already used by some physicians. Blood pressure dips can be avoided by intake of salt or fludrocortisone. Vascular regulation can be improved locally by carbonic anhydrase inhibitors, and systemically with magnesium or with low doses of calcium channel blockers. Experimentally, glaucomatous optic neuropathy can be prevented by inhibition of astrocyte activation, either by blockage of epidermal growth factor receptor or by counteracting endothelin. Glaucomatous optic neuropathy can also be prevented by nitric oxide-2 synthase inhibition. Inhibition of matrix metalloproteinase-9 inhibits apoptosis of retinal ganglion cells and tissue remodeling. Upregulation of heat shock proteins protects the retinal ganglion cells and the optic nerve head. Reduction of oxidative stress especially at the level of mitochondria also seems to be protective. This can be achieved by gingko; dark chocolate; polyphenolic flavonoids occurring in tea, coffee, or red wine; anthocyanosides found in bilberries; as well as by ubiquinone and melatonin. (**Surv Ophthalmol 52**:S174–S179, 2007.

Key words. activation of astrocytes • autoregulation • heat shock protein • metalloproteinase • neuroprotection • nitric-oxide synthase 2 • oxidative stress • systemic blood pressure • vascular regulation

For the past century glaucoma has been considered a disease for which diagnosis and treatment was focused mainly on reduction of intraocular pressure (IOP). Large studies such as The Ocular Hypertension Treatment Study and The European Glaucoma Prevention Study recognized ocular hypertension as the most important factor for the development of primary open-angle glaucoma (POAG). Because elevated IOP was associated with the development of glaucoma, and reducing IOP reduced the risk of visual field progression, IOP was considered a good surrogate for glaucoma treatment. The focus on IOP as the only risk factor, however, left several questions unanswered: Why do the majority of people with increased IOP not develop glaucomatous optic neuropathy (GON)? On the other hand, why do we see an increasing number of patients acquiring GON who have IOP in the normal range? Why does reduction of IOP, although on the average improving prognosis, not stop progression in all patients? And why do some patients need a very low IOP, indeed sometimes an even unphysiological low IOP, to stop progression of this disease? These questions can be answered when considering additional risk factors such as systemic hypotension or vascular dysregulation. The elucidation of these additional factors has lead to the investigation of non-IOP lowering treatment. Whether such treatment will be an adjunctive to the conventional IOP-lowering treatment (e.g., in patients with POAG) or whether it shall be used by itself (e.g., in patients with normal-tension glaucoma [NTG]) remains to be seen.

Some IOP-lowering glaucoma medications have additional effects. For example carboanhydrase inhibitors improve regulation of ocular perfusion. This review, however, will focus mainly on drugs that do not reduce IOP. Furthermore, we will discuss prevention of GON and only marginally deal with the prevention of IOP increase.

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In order to visualize the individual mechanisms that may be targeted by treatment we have recapitulated the figure of the pathogenic scheme by Flammer et al (Fig.1).[16] The section numbers which follow correspond to the numbers in Fig. 1.

Therapeutic Targets

1. INHIBITION OF ACTIVATION OF ASTROCYTES

The activation of the astrocytes in the optic nerve head (ONH) and retina plays an essential role in the pathogenesis of GON.[26,28,68] Both mechanical and ischemic stress can lead to activation of astrocytes. Once activated, astrocytes upregulate the production of various molecules, including matrix metalloproteinases (MMPs), nitric oxide synthase-2 (NOS-2), tumor necrosis factor-alpha (TNF-α), and endothelin, thereby creating an altered microenvironment leading to tissue remodelling and axonal damage.

1A. Inhibition of Epidermal Growth Factor Receptor (EGFR)

Mechanical stress leads to stimulation of EGFR, which, in turn, leads to activation of astrocytes and thereby to an upregulation of NOS-2. Blockage of EGFR, by a tyrosine kinase inhibitor, therefore prevents the activation of astrocytes.[38] Interestingly, such a treatment not only inhibits the activation of astrocytes but also leads to a reduction of loss of retinal ganglion cells. This indirectly indicates that the activation of astrocytes is relevant in GON.[28,45,68] Whether this approach will lead to glaucoma treatment in humans can at the moment not be predicted.

1B. Inhibition of the Effect of Endothelin-1

In glaucoma patients plasma concentration of endothelin-1(EN-1) is increased.[10] Endothelin not only further reduces optic nerve head blood flow and impairs anterograde and retrograde axoplasmatic transport,[59,62] but also activates astrocytes.[50] This is further supported by the fact that patients with vascular dysregulation more often have activated retinal astrocytes, which can be visualized clinically.[21,22] The effect of endothelin can be partially blocked by a number of different drugs such as calcium channel blockers (CCBs) including magnesium (a physiological CCB), dipyrimadole, or endothelin blockers.[7,18–20] Whether an inhibition of endothelin indeed also inhibits the activation of astrocytes has not yet been studied.

2. INHIBITION OF NITRIC-OXIDE SYNTHASE 2 (NOS-2)

Nitric oxide (NO), also known as the endothelium-derived relaxing factor, is biosynthesized from arginine and oxygen by various nitric oxide synthase (NOS) enzymes. There are three basic forms of NOS: neuronal nitric oxide synthase (nNOS or NOS-1), inducible nitric oxide synthase (iNOS or NOS-2), and endothelial nitric oxide synthase (eNOS or NOS-3).

NOS-2 leads to a marked production of nitric oxide. NOS-2 can be inhibited by the drug aminoguanidine, a nucleophilic hydrazine compound. Aminoguanidine is an oral insulin stimulant for type 2 diabetes mellitus. It further seems to prevent the formation of advanced glycation end products.[4] In addition, it is a relative specific inhibitor of NOS-2, which is why it was studied in experimental glaucoma. In experimental glaucoma aminoguanidine was capable of preventing the development of GON.[46] Such treatment appears very promising, but clinical studies are not yet available.

3. INCREASE OF SYSTEMIC BLOOD PRESSURE

Low blood pressure as well as nocturnal overdipping increases the probability of visual field deterioration.[32,64] We can therefore assume that an increase in blood pressure in patients with hypotension may improve prognosis although interventional studies supporting this view are rare. Treatment of hypotension with vasoconstrictive drugs although increasing blood pressure may further reduce blood flow. Blood pressure, however, can be increased with an increase in salt intake.[48] In severe cases the intake of the low-dosed fludrocortisone (0.1 mg/2× per week) has been described.[23] Fludrocortisone treatment not only slightly increases blood pressure and reduces nocturnal dips but also improves the regulation of blood flow indirectly.[23]

4. IMPROVEMENT OF VASCULAR REGULATION AND AUTOREGULATION

Vascular dysregulation is a major risk factor for GON.[15] Vascular regulation can be improved by various drugs. Among the IOP-lowering drugs, only carbonic anhydrase inhibitors (CAI) (in particular dorzolamide), have proven to both increase ocular blood flow (OBF) and improve the regulation of OBF,[44] thereby decreasing the chance of reperfusion injury.[17] Parallel to an improvement in OBF, an improvement in visual field was observed. Carbonic anhydrase inhibitors, like acetazolamide, improve visual fields in glaucoma patients.[13,14,47] Similar effects have been observed for CCBs. An improvement in OBF and visual function was only observed in patients with a vascular dysregulation.[24] Accordingly, a positive response to OBF on carbon-dioxide breathing predicts the effect of CCBs on OBF.[49] The effect of CCBs on visual field have also been

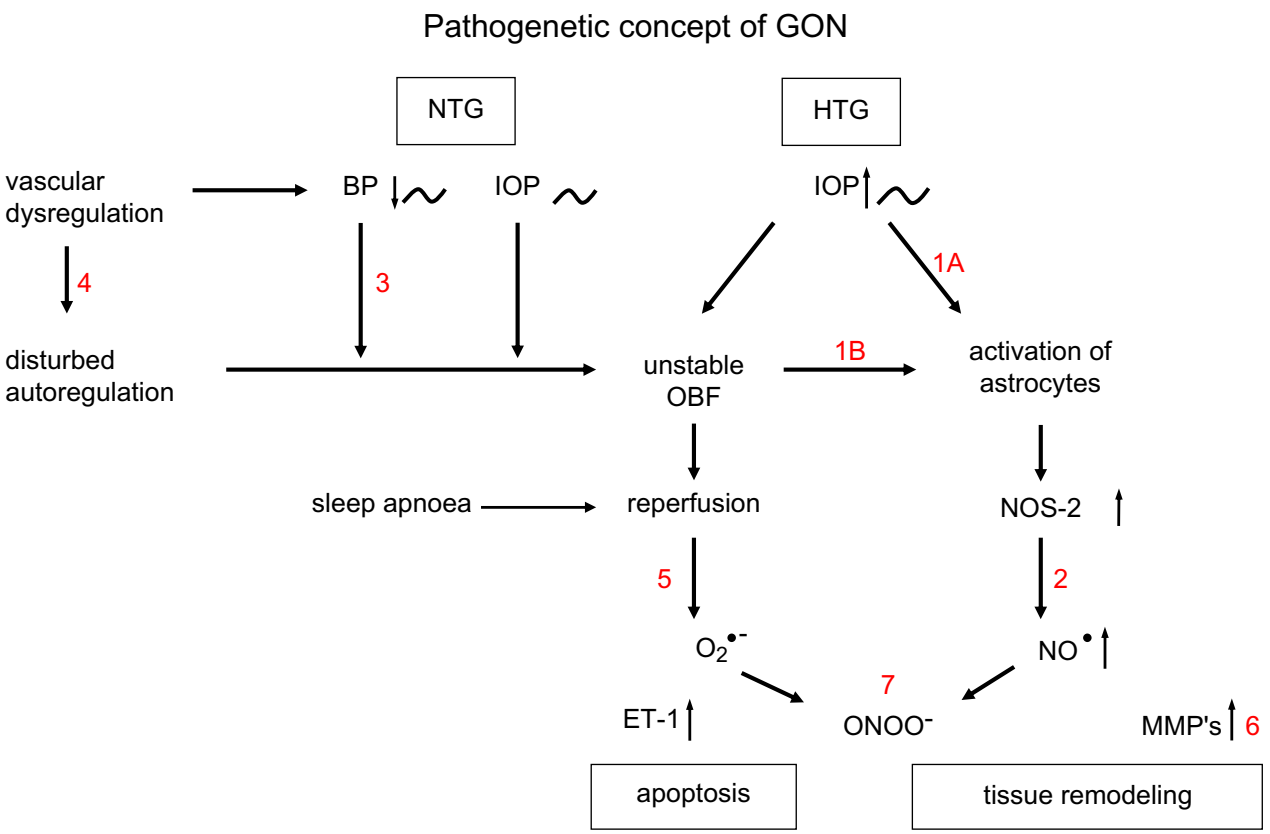

Fig. 1. The pathogenetic scheme by Flammer et al depicts the individual mechanisms that may be targeted by non-IOP lowering treatment. The numbers in red correspond to the section numbers in the manuscript (1 to 7 = 8). BP = blood pressure; IOP = intraocular pressure; NOS-2 = nitric oxide synthase-2; NO = nitric oxide; $ONOO^-$ = peroxynitrite; O_2^- = superoxide anion; MMP's = matrixmetalloproteinase. Based on: Flammer et al. What is the pathogenetic concept of glaucomatous optic neuropathy? Surv Opthal 52:S162–73, 2007.

demonstrated in masked double-blind studies.[36] Likewise, CCBs blocked the OBF-reducing effect of an endothelin infusion in healthy volunteers.[60] Dipyridamol, a drug often used in the past as a platelet inhibitor, also inhibits the effect of endothelin,[41] and improves OBF.[33] Unfortunately, the long-term role of dipyrimadole on glaucoma patients has not yet been studied. Among the systemic treatments, magnesium is a weak but harmless drug that partially inhibits the effect of endothelin[7] and improves blood flow.[19]

Omega-3-fatty acids (omega 3-FAs) have a number of different effects, including the modulation of intracellular calcium ion release and thereby the stabilization of circulation.[11] Omega 3-FAs also increase the production of uncoupling proteins and thereby improve ATP independent heat production, which is most probably impaired in patients with vascular dysregulation.[5,29]

Cacao beans from the seed of theobroma cacao contain a subclass of flavonoids, flavan-3-ols, which have been reported to augment eNOS, and thereby NO. This improves endothelium-dependent vasorelaxation.[34] Unfortunately the use of cacao beans has not yet been studied in the context of glaucoma.

5. COMBAT OF OXIDATIVE STRESS

Free radicals are involved in a number of inflammatory and degenerative diseases. Accordingly, oxidative stress is involved in the pathogenesis of GON where free radicals cause a damage to retinal ganglion cells and their axons.[12,63] In addition, oxidative stress leads to degeneration of trabecular meshwork (TM)[31,56,61] and thereby alterations in the aqueous outflow pathway, leading to increased IOP which, in turn, also damages retinal ganglion cells. The target of oxidative stress relevant in the development of GON are most probably the mitochondria.[1] It is therefore desirable to have a drug protecting the mitochondria, in particular the mitochondria of the optic nerve head.[1] This, unfortunately, cannot be achieved by an increase intake of vitamins such as vitamin C or vitamin E. Only molecules reaching the inner membrane of the mitochondria can be of potential use. Ginkgo

contains a number of substances, including polyphenolic flavonoids, that have been proven to protect the mitochondria from oxidative stress and thereby protect the retinal ganglion cells.[8,9,55,57] Moreover, ginkgo has been shown to improve visual fields in a long-term double-masked placebo-controlled study.[51] Efficacy and safety reports have suggested a daily dose of 120 mg to be sufficient and acceptable.[37]

There are a number of other naturally occurring substances that could theoretically be beneficial but have not been studied for glaucoma. Polyphenolic flavonoids have strong antioxidant capacity due to their free radical scavenging properties. Both green and black tea are rich sources of flavonoids such as catechin (C), epicatechin (EC), epigallocatechin (EGC).[52,66] Coffee also has good antioxidant properties due to polyphenolic compounds. In addition, coffee contains the molecule 3-methyl-1,2-cyclopentanedione (MCP), which has been shown to be a selective scavenger of the peroxynitrite.[35] Other naturally occurring compounds containing polyphenols include dark chocolate[42] and red wine.[27]

Anthocyanins, rich in foods such as bilberry, are another class of substances with antioxidant properties. In addition to polyphenolic rings, anthocyanins possess a positively charged oxygen atom in their central ring, which enables them to readily scavenge electrons.[39]

Ubiquinone (coenzyme Q10), is a coenzyme for the inner mitochondrial enzyme complexes involved in energy production within the cell with strong antioxidant properties. Coenzyme Q10 has been demonstrated to prevent lipid peroxidation and DNA damage induced by oxidative stress.[65] Ubiquinone has been studied well in dermatology but unfortunately studies of its use in glaucoma are lacking and therefore currently limit the use of this agent.

Melatonin (N-acetyl-5-methoxyryptamine) is an indoleamine, secreted by the pineal gland, which exerts antioxidant properties. Melatonin has been shown to neutralize free radicals.[3] In the retina, melatonin reduces the elevation of cGMP by suppressing NOS activity and thereby levels of NO, indicating a neuroprotective role. In addition, melatonin stimulates a number of antioxidative enzymes.[58]

6. INHIBITION OF METALLOPROTEINASE-9 (MMP-9)

MMP-2 and MMP-9 are upregulated in astrocytes of glaucoma patients.[2] MMP-9 is also upregulated in the circulating lymphocytes of glaucoma patients.[43] These MMPs, in particular MMP-9, are involved in both retinal ganglion cell loss and in tissue remodeling. MMP-9 can be inhibited pharmacologically by GM6001, also known as Ilomastat (N-[(2R)-2-(hydroxamidocarbonylmethyl)-4-methylpentanoyl]-L-tryptophan methylamide). Studies reveal that inhibition of MMP-9 with GM6001 prevents retinal ganglion cell loss in an animal model.[40] Moreover, MMP-9 knock-out mice do not show apoptosis of retinal ganglion cells even when the optic nerve is ligated.[6] MMP-9 most probably plays a role in the pathogenesis of GON.

7. STIMULATION OF HEAT SHOCK PROTEIN (HSP) PRODUCTION

Heat shock proteins (HSPs) are produced by different cells when subjected to stress (e.g., elevated temperatures or oxidative stress). The upregulation of these proteins is a protective mechanism as they act as molecular chaperones protecting the three-dimentional structure of other proteins. In a rat model, pharmacologically induced upregulation of HSPs by the systemic administration of the compound geranylgeranylacetone (GGA) protected retinal ganglion cells from glaucomatous damage.[30] Whether treatment with this drug or the natural stimulation of HSPs (e.g., by sauna baths) is beneficial in humans, needs to be studied.

8. NEUROPROTECTION

The term neuroprotection is not well defined. All the previously mentioned treatments can also be considered neuroprotectants in a broad sense. One of the drugs often referred to in this context is memantine. Memantine is classified as an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, binding near the Mg^{2+} site within the ion channel. Uncompetitive antagonists physically block the channel in the NMDA receptor through which ions flow by occupying it. Memantine has been shown (in a randomized, placebo-controlled study) to be clinically effective in the treatment of the neurodegenerative Alzheimer disease.[53] Moreover, it has been shown to provide structural protection to retinal ganglion cells in a primate model of glaucoma.[25,67] The clinical value of this, in human glaucoma, is still under investigation.

Conclusion

Theoretically, a number of options are available to treat glaucoma. The different risk factors known lead through the same or similar pathomechanisms to GON. Therapeutically, we can either eliminate or mitigate risk factors or target defined pathogenic steps. Risk factors that can be influenced include

increased IOP, low blood pressure, and vascular dysregulation. Pathogenic steps that can be targeted include activation of astrocytes, upregulation of NOS-2 or MMPs. At the moment any type of clinical or experimental treatment is based on the prevention of GON. A restoration of damaged optic nerve is at the moment not yet possible at all. Already, many of these new treatment strategies have proven to be likely beneficial in humans.[54] For those remaining, further rigorous investigation is deserved to open up a new therapeutic era in glaucoma.

Method of Literature Search

A systematic search of the Medline database using the PubMed Web site (through 2007) was conducted using the following key words: *non-IOP lowering treatment, POAG, oxidative stress, reactive oxygen species, astrocytes, epidermal growth factor receptor, tyrosine kinase inhibitor, Endothelin-1, Endothelin blockers, calcium channel blockers, dipyrimadole, nitric oxide synthase-2, aminoguanidine, fludrocortisone, carbonic anhydrase inhibitors, calcium channel blockers, omega-3-fatty acids, polyphenolic flavonoids, anthocyanosides, gingko, dark chocolate, tea, coffee, red wine, ubiquinone and melatonin, metalloproteinase-9, heat shock proteins.* All articles read were in English and when articles in other languages were of relevance, their abstracts in English were read.

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Reprint address: Josef Flammer, MD, University Eye Clinic Basel, Mittlere Strasse 91, P.O. Box, CH-4031 Basel, Switzerland.