Review Article

Neuroprotection in glaucoma

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Neuroprotective therapies in glaucoma may play a role in preventing ischemia and oxidative damage that results in apoptosis of retinal ganglion cells and optic nerve damage. Although intraocular pressure (IOP) is the only known modifiable risk factor for glaucoma, disease progression commonly occurs despite IOP control, suggesting that factors other than IOP play a role in its pathogenesis and can potentially act as targets for neuroprotection. Factors including mediators of apoptosis, ischemic changes, poor ocular blood flow and neurotoxins have been hypothesized to play a role in glaucoma progression. Neuroprotective targets include glutamate-induced neurotoxicity, nitric oxidase synthetase, neurotropins, calcium channel receptors, free radicals, vascular insufficiency, the rho-kinase pathway, and more. Drugs related to these factors are being evaluated for their role in neuroprotection, although this area of investigation faces several challenges including limited evidence for these agents' efficacy in clinical studies. Additionally, while IOP-lowering therapies are considered neuroprotective as they generally slow the progress of glaucoma progression, they are limited by the extent of their effect beyond IOP control. The aim of this article is to review the current treatment options available for neuroprotection and to explore the drugs in the pipeline.

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Glaucoma is the leading cause of irreversible blindness in both developed and developing nations[1] and its prevalence is projected to increase to 111.8 million by 2040.[2] It is a chronic disease characterized by progressive optic neuropathy caused by damage to the retinal ganglion cells (RGCs) resulting in typical structural and functional defects.[3] RGC damage results from multifactorial causes including intraocular pressure (IOP) elevation, ischemia/reperfusion damage, oxidative/nitrosative stress, neurotrophic growth factor deprivation, activation of autoimmunity, and glutamate neurotoxicity. Till date, the only modifiable risk factor for glaucoma is elevated IOP; hence, both medical and surgical treatment options aim to reduce the IOP in an effort to arrest glaucoma progression. However, recent evidence suggests that optic nerve damage can continue despite effective lowering of IOP.[4-6] As RGCs cannot divide and regenerate, optic nerve damage is irreversible; therefore, neuroprotective strategies to preserve RGCs and optic nerve neuronal structure and function are imperative.[7,8] Although IOP reduction is still considered the most promising mechanism to protect the optic nerve from glaucomatous damage, neuroprotective agents under investigation include N-methyl D-aspartate (NMDA) receptor antagonists, antioxidants, Gingko biloba extract, and more. The aim of this review is to discuss the role of various neuroprotective agents based on the available literature.

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Methods

A detailed search of databases includes Pubmed, Medical Subject Headings Cochrane library, and Embase. The search was conducted with the following keywords: neuroprotection in glaucoma, pharmacological agents for glaucoma, antioxidants, newer drugs for glaucoma, neuromodulators, and ocular blood flow.

Pathophysiology of glaucoma and the role of neuroprotection

Glaucoma is a neurogenerative disease that is characterized by typical structural defects of the optic nerve and resulting functional defects of the visual field. These defects occur when RGCs that are grouped at the optic nerve undergo apoptosis.[3] RGC and axonal injury in glaucoma is due to multiple causes, of which elevated IOP is a predominant factor. IOP elevation leads to distortion of the lamina cribrosa, which in turn leads to axoplasmic stasis, preventing neurotropic factors from the brain from reaching the RGCs. Although IOP plays an important role in the pathogenesis of glaucoma, it is not the only factor. This was demonstrated in multiple randomized clinical trials including the Ocular Hypertension Study,[9] in which progression was not seen despite IOPs as high as 32 mm Hg, and the Collaborative Normal Tension Glaucoma Study,[4] in which progression was seen with IOPs below 21 mm Hg. These observations further support the theory that factors other than IOP may play a role in pathogenesis of glaucoma. For instance, normal

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tension glaucoma constitutes a significant proportion of open angle glaucoma, and is characterized by typical glaucomatous optic neuropathy despite low IOPs (10–21 mm Hg) at all time points.[10-13] These eyes are postulated to undergo ischemia, leading to an increase in excitotoxic substances such as glutamate in the vitreous, which activate the NMDA receptor and results in a cascade of events that induces apoptosis [Fig. 1].[14]

Neuroprotective requirements

Neuroprotection refers to the treatment of disease by preventing neuronal death or deterioration.[15] Neuroprotective targets include glutamate-induced neurotoxicity, nitric oxidase synthetase, neurotropins, calcium channel receptors, free radicals, vascular insufficiency, and rho-kinase (ROCK) pathway; drugs related to these factors are being evaluated as potential treatment options.[16,17] Neuroprotective treatment has been approved for central nervous system diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and other neurodegenerative diseases.[18] Neuroprotective therapies in glaucoma may play a role in preventing ischemia and oxidative damage that results in apoptosis of RGCs and optic nerve damage.

To evaluate the potential clinical applicability of a pharmacological agent as a neuroprotectant in glaucoma, four criteria have been proposed.[19]

1. There must be specific target receptors in the retina or optic nerve.
2. There must be laboratory evidence to support that it has a mechanism of action that enhances neuronal resistance to injury.
3. It must be available at the retina or optic nerve at pharmacological concentrations required for a neuroprotective effect.
4. It must have demonstrated neuroprotective activity in prospective randomized clinical trials.

Pharmacological agents

1. ***Antiglaucoma Medications***
   a. Alpha-2 adrenergic agonists
   b. Prostaglandin analogues
   c. Beta blockers
   d. Carbonic anhydrase inhibitors
   e. ROCK inhibitors
2. ***Antioxidants***
   a. Gingko biloba extract
   b. NMDA receptor antagonist
   c. Citicoline
   d. Melatonin
   e. Crocus sativus
3. ***Vasodilators***
   a. Calcium channel blockers (CCBs)
   b. Carbonic anhydrase inhibitors.

Antiglaucoma medications

The primary modality of treatment in the management of glaucoma still remains the antiglaucoma medications. The most probable mechanism by which the available antiglaucoma medications offer neuroprotection is by lowering of IOP itself.

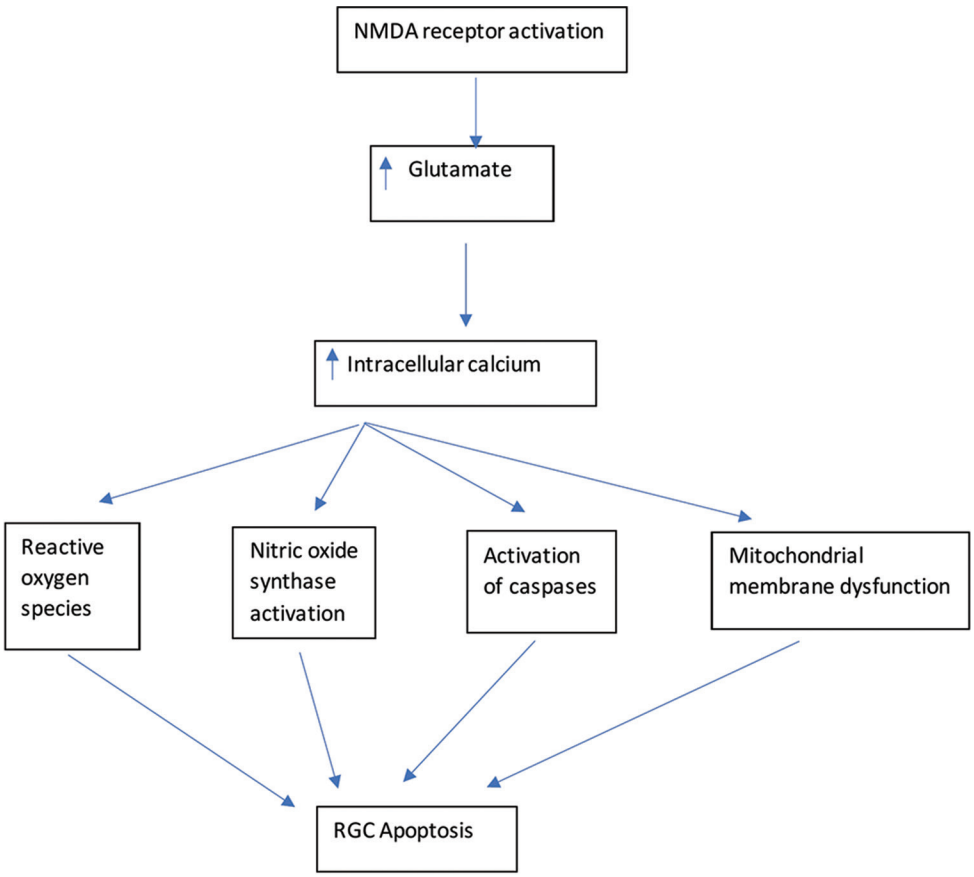

Figure 1: NMDA receptor activation pathway–excitotoxicity pathway leading to RGC apoptosis

Alpha-2 adrenergic agonists

Brimonidine tartrate, a third generation alpha-2 adrenergic agonist, is hypothesized to provide neuroprotective effects through its antiapoptotic properties, though the exact mechanism still remains unclear.[20,21] Brimonidine generally causes vasoconstriction but causes vasodilation on retinal arterioles and increases ocular blood flow.[22] Studies on the effect of brimonidine on experimental animal models of optic nerve injury provide further evidence of its neuroprotective potential. A preclinical study compared RGC survival following subcutaneous administration of brimonidine vs. timolol in a chronic ocular hypertensive rat model.[23] In brimonidine-treated eyes, RGC survival was 50% more likely as compared to timolol-treated eyes. Additionally, the Low Pressure Glaucoma Treatment Study randomized normal tension glaucoma patients to treatment with brimonidine vs. timolol and found that despite an identical effect on IOP, patients treated with brimonidine were less likely to have visual field progression than those treated with timolol.[24] Likewise, a small randomized controlled trial of newly diagnosed glaucoma patients found that those randomized to brimonidine treatment had an improvement in contrast sensitivity as compared to those randomized to timolol. This effect appeared to be independent of IOP-lowering effects, supporting a neuroprotective mechanism.[25]

Prostaglandin analogues

Since their introduction in the 1990s, prostaglandin analogues have been a first-line drug for glaucoma treatment as they offer substantial IOP reduction achieved with once daily dosing and the relative absence of systemic side effects as compared with other monotherapies. Prostaglandins have also demonstrated better control of IOP fluctuation over a 24-h period than beta blockers.[26,27] Additionally, latanoprost has shown neuroprotective effect on glutamate-induced RGC death *in vitro* and ischemic or axotomy-induced optic neuropathy mimicking glaucoma in animal models.[28] Latanoprost has also demonstrated increased optic nerve head blood circulation in rabbits, monkeys, and normal humans; this appears to be independent of an IOP-reducing effect.[29] Latanoprost is believed to exert its neuroprotective effects by impeding glutamate and hypoxia-induced apoptosis and act via negative feedback on cyclooxygenase-2 activity.

Ocular perfusion pressure (OPP) is equal to two-third mean blood pressure minus IOP, is an important determinant of ocular blood flow, and 24-h OPP fluctuation is known to be a risk factor for normal tension glaucoma.[30,31] A randomized controlled trial comparing latanoprost and bimatoprost found that both prostaglandins demonstrated significant IOP reduction, but latanoprost was associated with improved OPP, whereas bimatoprost did not show this effect.[32,33]

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors lower IOP by blocking the enzyme carbonic anhydrase, which is essential for the production of the aqueous humor. In addition, carbonic anhydrase inhibitors have an influence on the buffer system of the body, reducing pH, and inducing vasodilation.[34] Vasodilation in turn increases retinal perfusion; these mechanisms might lead to an additive neuroprotective effect beyond IOP control. A study comparing timolol vs. dorzolamide in a rat glaucoma model found that both classes of medication led to a significant IOP reduction and RGC preservation. However, the level of neuroprotection conferred by dorzolamide correlated with the level of IOP reduction, which suggests an IOP-dependent path to neuroprotection rather than intrinsic neuroprotective properties.[35] Both dorzolamide and brinzolamide have shown to have increased end diastolic velocity and OPP on ocular blood flow analysis.[36]

Beta blockers

The neuroprotective effect of betaxolol and the nonselective β-blockers metipranolol and timolol are thought to be elicited through reduction in sodium and calcium influx through voltage sensitive channels, which are responsible for ischemia/reperfusion injury and are linked to the release of glutamate and subsequent activation of NMDA receptors.[37,38] Levobetaxolol has been found to be a more effective neuroprotectant than timolol, likely due to its greater capacity to block sodium and calcium influx.[39] The improvement in both neurological and histological outcomes in transient cerebral ischemia following administration of β-adrenoreceptor antagonists is partly attributed to attenuation of glutamate release. Betaxolol has also been demonstrated to increase blood velocity in the human optic nerve head, thus supporting the hypothesis that mediation of vasculature effects may temper ischemia-induced RGC injury.[40] Additionally, betaxolol and levobunolol's role in neuroprotection is mediated by blockade of voltage-gated calcium channels[41]; timolol and carteolol also exhibited similar actions albeit to a lesser degree.[42]

Rho-kinase inhibitors

ROCK are serine/threonine kinases that play an important role in fundamental processes of cell migration, proliferation and survival.[43] Blockade of ROCK promotes axonal regeneration and neuroprotection. Elevated levels of rho enzymes have been found in the optic nerve head of glaucomatous eyes as compared with age-matched controls, supporting a possible role for rho in glaucomatous neuropathy. Both fasudil and netarsurdil have been reported to arrest axonal degeneration, promote axonal regeneration,[44] and have been found to increase ocular blood flow.[45] While neuroprotective activity of ROCK inhibitors has been demonstrated in the eye, further studies are warranted.

Antioxidants

Ginkgo biloba extract

Ginkgo biloba is a native tree of China with various uses in traditional medicine. Leaf extract of Gingko biloba has antioxidant and vasoactive properties and may play a role in combating oxidative damage and apoptosis-mediated damage to the optic nerve head in glaucoma. In a clinical study on 52 primary open-angle glaucoma patients who were followed for 3 months, those treated with Gingko biloba extract showed a relevant decrease of endothelin-1 resulting in vasodilation. This was paralleled by a decrease of malondialdehyde-modified low-density lipoproteins and plasma malondialdehyde levels, indicating the activation of an antioxidant response and the attenuation of oxidative stress.[46]

NMDA receptor antagonists

Increased levels of glutamate and glutamine (metabolic precursor) and decreased levels of the glutamate transporter

excitatory amino acid transporter 1 have been reported in the vitreous and retinal mounts of patients with glaucoma compared with healthy individuals.[47] This suggests an association between the excessive release of glutamate in the retina, neuronal cell death, and glaucoma.[48] Excess glutamate activates the NMDA receptor, leading to influx of calcium followed by stimulation of proapoptotic factors. Thus, NMDA receptor blockade is a potential target to prevent apoptosis, but NMDA receptor activity is essential for normal neuronal function. Memantine is a noncompetitive NMDA open-channel blocker, meaning it will block only excess NMDA receptors that are activated by glutamate without affecting their normal activity. Memantine was considered a promising neuroprotective drug for glaucoma during *in vitro* studies,[49,50] but two randomized, placebo-controlled multicentre trials did not find any significant difference between patients on memantine and placebo in preventing visual field progression.[51]

Cytidine-5'-diphosphocholine (Citicoline)

Citicoline is a naturally occurring cell endogenous compound, intermediate in the synthesis of membrane phospholipids such as phosphatidylcholine.[52] Experimental studies have shown that citicoline may increase the synthesis of phospholipids in the CNS and has a neuromodulator effect, potentially leading to a protective effect on RGCs.[52] A beneficial effect of citicoline oral supplement has been demonstrated in patients with nonarteritic ischemic optic neuropathy.[53] Additionally, a multicenter study on oral citicoline supplementation in patients with progressive glaucomatous visual field loss found a reduction in the mean rate of visual field progression from −1 dB/year to −0.15 (±0.3) dB/year over a 2-year period.[52]

Melatonin

Melatonin is a hormone ubiquitously distributed in living systems from bacteria to plants and animals.[53] In mammals, including humans, melatonin is secreted during darkness by the pineal gland and is inhibited by light, allowing for the modulation of the body's sleep pattern.[54] It is reported to have antioxidant and antiscavenging properties.[55] Recognizing its potential beneficial antioxidant and ocular hypotensive properties, several melatonin-related compounds, such as synthetic analogues and specific agonists of melatonin receptors, are underinvestigation.[56] Among the melatonin analogues, agomelatine is currently attracting interest for its pharmacological activities in both animal and human trials as it has shown both IOP-lowering and antioxidant properties.[57,58]

Crocus sativus (Saffron)

Saffron is derived from the pistils of *Crocus sativus* and contains high concentrations of the carotenoids crocin and crocetin. In a model of rat brain cerebral contusion, crocetin's protective effects were related to its proangiogenic and antiapoptotic activities.[59] Crocin is thought to improve both the retinal and the choroidal blood flow *in vivo* and consequently facilitates retinal function recovery following IOP increase.[60]

Vasodilators

Calcium channel blockers

CCBs are drugs that alter calcium influx across cell membranes and intracellular calcium levels. Although their primary indications are treatment of angina pectoris, essential hypertension, and certain arrhythmias, CCBs also have clinical potential for ameliorating the IOP-independent destructive processes in open angle glaucoma. CCBs generally dilate isolated ocular vessels and increase ocular blood flow in

Summary

Drug	Neuroprotection mechanism	Current status
Beta blockers[37,38]	Arrests retinal ischemia allows for vasodilation, blocks glutamate release, and activation of NMDA receptors	Betaxolol preferred over timolol due to vasodilation and increased blood flow
Alpha agonists[22]	Vasodilation on retinal arterioles, increasing ocular blood flow	Routinely used but commonly has local side effects like follicular conjunctivitis
Prostaglandins[30,31]	Blocks glutamate-induced apoptosis and hypoxic damage causes vasodilation	Has the best hypotensive effect and also increases ocular blood flow and antiapoptotic actions, especially latanoprost
Carbonic anhydrase inhibitors[34,35]	Increased ocular blood flow *in vivo* studies	Less effective in healthy subjects, as neuroprotection is correlated with IOP reduction
Rho-kinase inhibitors[44,45]	Arrest axonal degeneration and promote axonal regeneration through rho-kinase inhibition, also causes vasodilation	Has shown promising results in studies. Are under evaluation
NMDA antagonist[49,51]	NMDA receptor blockade, acts as an antioxidant, prevents apoptosis	Was not effective on clinical trials
Calcium channel blockers[61]	Vasodilation of ocular vessels increases ocular blood flow	Promising results in in-vivo studies, need further evaluation
Citicoline[52]	Increases the synthesis of phospholipids -protective role on RGCs	Can be used as oral supplement along with an ocular hypotensive agent
Ginkgo biloba extract[46]	Antioxidant, decreases endothelin-1 causing vasodilation	May be an adjuvant therapy for NTG and for high-tension glaucoma patients progressing despite a normalized IOP
Melatonin[55,57]	Antioxidant, agomelatine has shown to reduce IOP	Shown promising results in animal studies. Under evaluation in human trials
Crocus sativus[59,60]	Improves both the retinal and the choroidal blood flow *in vivo* studies, antioxidant	Promising results *in vivo* studies

experimental animals, normal humans, and patients with open-angle glaucoma.[61] Drugs including lomerizine and nilvadipine have shown promising neuroprotective results in *in vivo* studies. However, there are concerns regarding CCB-related systemic hypotension, as these agents can worsen retinal ischemia due to a reduction in OPP.[61]

Stem cell therapies

The use of mesenchymal and human embryonic stem cells is an area of research in glaucoma neuroprotection. While mesenchymal stromal stem cells have demonstrated an association with neuroprotective factors such as platelet-derived growth factor, the stem cell injection itself may lead to significant negative posterior segment outcomes including reactive gliosis of the optic nerve, retina, and additionally vitreous clumping.[62,63] Additionally, studies have demonstrated successful differentiation of human embryonic stem cells into RGCs as well as integration of these transformed cells into the host retina.[64,65] Several clinical trials are ongoing, but this field contains several inherent challenges from scientific and ethical perspectives.

Conclusion

Although there has been increasing interest in neuroprotective therapies for glaucoma, this area of investigation faces several challenges. Preclinical studies on animal models of neurodegeneration have demonstrated promise in the use of NMDA receptor blockers, alpha-2 adrenergic agonists, CCBs, antioxidants, Gingko biloba extract, stem cell therapies, and others. However, only a few approaches have been able to be translated into clinical trials in humans, and there is a lack of evidence for these agents' efficacy in clinical studies.[66] Head-to-head comparison of conventional treatment and neuroprotective therapies is needed to demonstrate the benefits of neuroprotection as compared to conventional therapy. Additionally, while IOP-lowering therapies generally slow the progress of glaucoma progression, they are limited by the extent of their effect beyond IOP control. Furthermore, clinical studies are necessary to assess the role of neuroprotective therapies in preventing glaucoma development and progression in individuals with a genetic predisposition to glaucoma. Nonclinical and clinical studies on non-IOP dependent neuroprotective therapies for glaucoma are growing, and some of these may result in novel drugs approved for clinical use. Despite the promising results from nonclinical studies, RGC protection remains a challenge to both scientists and clinicians.

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Conflicts of interest

There are no conflicts of interest.

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