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Review Article

GLAUCOMA MANAGEMENT BEYOND IOP: THE ROLE OF NEUROPROTECTIVE DRUGS

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Abstract

Glaucoma, a progressive optic neuropathy marked by irreversible vision loss and optic nerve damage, remains a leading global cause of blindness. The current treatments mainly target intraocular pressure (IOP) reduction to slow damage to optic nerve progression, growing research emphasizes neuroprotection, a mechanism beyond IOP control. This review explores the role of neuroprotection of antiglaucoma medications, focusing on mechanisms such as glutamate regulation, mitochondrial protection, oxidative stress reduction, and neurotrophic factor support. It also focuses on challenges in translating preclinical insights into clinical practice and examines ongoing trials. Considering neuroprotective strategies with standard treatments could improve outcomes and reduce the disease burden.

INTRODUCTION

With a rising prevalence, glaucoma is one of the main causes of permanent visual loss in the world.[1] A group of disorders known as glaucoma include progressive damage to the optic nerve, loss of retinal ganglion cells, and a slow deterioration of peripheral vision.[2] One of the main clinical characteristics of glaucoma is elevated intraocular pressure (IOP), which is also the sole risk factor for the disease progression that may be changed. Long-term usage of eye drops might have adverse consequences and be expensive, and surgical procedures might not always be effective. Further, even with successful IOP management, glaucoma can worsen so the need for advanced therapies that directly prevent degeneration of the retina and optic nerve.

According to experimental research, glaucoma-related neurodegeneration results from interactions between vascular, metabolic, oxidative, biomechanical, and inflammatory variables. RGCs are primarily affected by two stressors: aging and high intraocular pressure (IOP). RGC depletion linked to glaucoma is significantly influenced by microglia, the central nervous system.

The main goal of current glaucoma treatment is to reduce intraocular pressure (IOP), however even when this modifiable risk factor is effectively managed, disease progression may still occur.[3]

Experimental studies suggest that glaucoma-related neurodegeneration arises from interrelated pathological mechanisms, including biomechanical, vascular, metabolic, oxidative, and inflammatory factors. Glaucoma treatment primarily target reducing intraocular pressure (IOP), yet disease progression may persist even with effective control of this modifiable risk factor.[4]

When evaluating neuroprotector medicines for glaucoma, four important criteria are used. The drug must first target receptors in the optic nerve or retina selectively. Second, experimental data showed improved neurological damage that may confirm its mode of action. Third, after topical delivery, the drug must reach the retina or optic nerve in pharmacologically effective concentrations. Lastly, prospective randomized clinical trials are required to confirm neuroprotective effectiveness. These substances have the potential to slow down the progression of glaucoma and preserve retinal ganglion cell (RGC) activity, providing a basis for neuroprotective therapeutic approaches.

The ability of neuroprotective medicines to function as pharmacological antagonists and correct imbalances between cell death and survival signals in order to prevent RGC death and optic nerve injury provides the therapeutic justification. Neuroprotection can also help maintain visual function and encourage self-repair by focusing on the

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mechanisms that underlie RGC loss, which addresses the terminal process in the pathophysiology of glaucoma.[5] The precise cause of glaucomatous optic neuropathy is still up for debate.

Classification of Neuroprotection Drugs:

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

1. α2-adrenergic agonists

α2-adrenergic agonists decrease intraocular pressure (IOP) via blocking adenylate cyclase, which lowers cAMP levels and, in turn, lowers the formation of aqueous fluid.[6] Additionally, these medications enhance uveoscleral outflow, which lowers intraocular pressure (IOP) even more.[7] The possible neuroprotective effects of α2-adrenergic agonists are still of interest despite their extensive usage in the treatment of glaucoma. Brimonidine applied systemically may help reduce optic nerve and retinal degeneration linked to ocular hypertension, according to research.[8]

Additionally, brimonidine contributes to the activation of pro-survival pathways and endogenous molecules such brain-derived neurotrophic factor (BDNF).[9] It has also been connected to the increased expression of a number of pro-survival factors in the retina, such as the PI3K/Akt signaling pathway, the extracellular signal-regulated kinases (ERKs), the anti-apoptotic proteins Bcl-2 and Bcl-xl, and the vascular basement membrane protein bFGF.[9]

Brimonidine's neuroprotective action may include modulating RGC, NMDA receptors. The drug also resulted in a significant decrease in cytosolic apoptotic calcium signals and NMDA-induced whole-cell currents.[10]

2. Beta Blockers

The most widely used medications to reduce intraocular pressure (IOP) in glaucoma are topical β-adrenoceptor blockers. Their main method of action is blocking β-adrenoceptors, which lowers the generation of aqueous humor.[11]

According to a 2003 study, betaxolol therapy considerably reduced the decrease in retinal choline acetyltransferase immunoreactivity and the thickness of the inner plexiform layer following ischemia/reperfusion injury. According to these findings, betaxolol functions as a neuroprotective drug that protects retinal cells from ischemia induced damage.[12,13]

According to a 2005 study, dorzolamide and timolol both significantly decreased intraocular pressure (IOP) and assisted in reversing the loss of retinal ganglion cells (RGCs). In the group treated with dorzolamide, there was a significant correlation between RGC count and IOP, but not in the other groups.[14]

It has been demonstrated that betaxolol maintains synaptic connections in ischemia damage models. By minimizing cell death and maintaining retinal function following injury, timolol has shown protective effects on retinal ganglion cells (RGCs), β-blockers' neuroprotective processes also include controlling sodium and calcium channels, which affect glutamate release and ion influx, which in turn activates NMDA receptors.[14,15]

3. Prostaglandin Analogs

Because prostaglandin analogues can effectively lower intraocular pressure with a single daily dose, they are frequently employed as the first-line treatment for glaucoma. They provide a well-tolerated alternative with few systemic side effects by increasing uveoscleral outflow.[16]

According to pharmacological data, bimatoprost lowers intraocular pressure by targeting prostamide receptors in the trabecular meshwork, which is where uveoscleral outflow occurs.[17]

Additionally, by lowering apoptotic retinal ganglion cell (RGC) death after optic nerve injury, prostaglandin analogs such as latanoprost show secondary neuroprotective effects in glaucoma. It is believed that this action, which shields cells from glutamate-induced toxicity, happens through negative feedback on the COX pathway.[13,18]

4. Carbonic Anhydrase Inhibitors

The primary isoenzyme in the anterior segment of the eye that produces aqueous humor is carbonic anhydrase II (CA-II). Aqueous humor levels are considerably decreased by carbonic anhydrase inhibitors, such as Brinzolamide and Dorzolamide, which efficiently inhibit it. Another CA inhibitor, acetazolamide, targets CA-II to reduce intraocular pressure by reducing the ciliary epithelium's production of bicarbonate.[19]

In retinal tissue exposed to methylglyoxal and glyoxal, intermediates of advanced glycation end products, these drugs have been demonstrated to decrease apoptotic pathways.[20]

Additionally, CA inhibitors have vasodilatory effects that could improve blood flow to the brain and eyes. Additionally, they have the ability to alter the pH of extracellular fluid,[21] which may have an impact on metabolic activity.

Research has demonstrated that: A 60-month study carried out in 2009 found that patients with primary open-angle glaucoma (POAG) experienced a considerable increase in retrobulbar blood flow when dorzolamide 2% and timolol 0.5% were taken twice daily.[22] A 2010 study showed that glaucoma patients' visual fields remain unchanged when their ocular blood flow improves over the years.[23]

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Additionally, after taking dorzolamide, the amplitude of the ocular pulse increase.[24,25]

5. NDMA Antagonist

Numerous phases of neurodegeneration have been linked to excitotoxicity caused by excess glutamate and glutamate receptor stimulation. By directly stopping already metabolically stressed neuronal cell types from reacting to excess glutamate, NMDA receptor antagonists most likely prevent more damage and cell death.[26]

When given systemically before to or within 30 minutes of retinal ischemia, the NMDA receptor antagonist memantine decreased ganglion cell loss in a 1998 study that used a rat model of pressure-induced ischemia.[27]

It was discovered that systemic administration of memantine, a substance that does not decrease intraocular pressure, was both safe and successful in minimizing the functional loss linked to experimental glaucoma.[28]

Systemically administered memantine and dizocilpine showed a neuroprotective effect against experimental glaucomatous optic neuropathy in rats in a study conducted in 2000.[29]

6. Rho Kinase Inhibitors

By focusing on the Rho kinase (ROCK) pathway, which is essential for cytoskeletal dynamics, axonal transport, and neuronal survival, new treatments such as ripasudil exhibit potential in neuroprotection. It has been demonstrated that inhibiting ROCK enhances neuroprotection and axonal regeneration. Rho enzyme participation in glaucomatous neuropathy is suggested by elevated Rho enzyme levels in the optic nerve head of glaucomatous eyes. It has been shown that both netarsudil and fasudil can enhance ocular blood flow, encourage axonal regeneration, and stop axonal degradation.[30]

According to a 2024 study, topical ripasudil helped restore retinal ganglion cells (RGCs) following optic nerve damage by suppressing the production of TNFα, IL-1β, and monocyte chemotactic protein-1. Additionally, the study showed that ripasudil plus brimonidine was more effective than either medication alone.[31]

7. Citicholine

Citicoline enhanced neuronal conduction and retinal function in glaucoma patients with moderate visual impairments. Visual impairment was considerably slowed, maintained, or even improved with long-term treatment (two to eight years).[32,33]

Additionally, oral citicoline treatment was reported to reduce the short-term loss of the average retinal nerve fiber layer in patients with primary open-angle glaucoma (POAG). According to study results, citicoline may significantly decrease the progression of glaucoma.[34,35]

In an experimental model of glaucoma, citicoline has been shown to be effective in protecting the visual pathway's axons.[36]

Patients receiving citicoline showed significant improvements in both vision field and retinal nerve fiber layer thickness, confirming the medication's neuroprotective properties.[37] The electrophysiological response significantly improved after citicoline administration, according to an electrophysiological investigation that used standard electroretinogram (PERG) and visually evoked potential (VEP). This improvement lasted even after the washout period.[38]

8. Calcium Channel Blockers

In healthy people, open-angle glaucoma patients, and experimental animals, calcium channel blockers (CCBs) usually widen ocular arteries and enhance ocular blood flow. In vivo studies have demonstrated promising neuroprotective effects of medications such as nilvadipine and lomerizine. However, there are concerns that systemic hypotension linked to CCB might aggravate retinal ischemia by lowering ocular perfusion pressure (OPP). In spite of this, there is substantial evidence to support the use of CCBs as a treatment for glaucoma.[39]

When compared to a placebo, oral nimodipine improved color sensitivity and visual fields in patients with normotensive glaucoma. This effect was probably caused by vasodilation, which increased ocular blood flow to the optic disc.[40,41]

In patients with glaucoma, other calcium channel blockers (CCBs), such as nilvadipine and brovincamine, have also demonstrated improvements in vision.

9. Antioxidants

Reactive oxygen species (ROS) in cells can be directly neutralized by administering antioxidants, which lowers oxidative damage. Research on the application of antioxidants in glaucoma, including results from both human and animal models, is compiled in this review.

a) Melatonin and its analogues

In newborn rats, melatonin has been demonstrated to prevent hypoxia-induced retinal ganglion cell loss.[42]

Another important element in the onset and progression of glaucomatous optic nerve injury is impaired blood flow in the eyes.[43] Further damage can result from disruptions in the oxygen supply to retinal ganglion cells (RGCs) caused by changes in blood pressure or intraocular pressure (IOP).[44]

Melatonin's vasoactive qualities and capacity to control arterial vasoconstriction can help improve these problems by affecting the regulation of blood flow and intraocular pressure.[45]

In rabbits with normal and increased intraocular pressure, agomelatine has been demonstrated to lower intraocular pressure.[46] According to a clinical study, patients with primary open-angle glaucoma (POAG) get a hypotensive response with oral agomelatine. Following 15 and 30 days of agomelatine treatment, there was a steady and noticeable drop in ocular pressure.[47]

b) Ginkgo biloba (GB) extract

It was demonstrated that a rat retinal ganglion cell (RGC) line treated with ginkgo biloba (GB) extract had a higher survival rate after being exposed to hydrogen peroxide-induced oxidative stress.

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In patients with normal-tension glaucoma (NTG), ginkgo biloba (GB) extract has been demonstrated in numerous clinical investigations to improve vision and slow the course of visual field degradation.[48,49] Individuals with normal-tension glaucoma (NTG) who took 80 mg of ginkgo biloba (GB) extract tablets twice daily for four weeks showed notable changes in ocular blood flow, volume, and speed when compared to those who received a placebo, which was consistent with the vascular theory of glaucoma development.[50]

Miscellaneous Antioxidants

In primary open-angle glaucoma (POAG), a variety of studies have demonstrated that antioxidants, such as vitamins B3, C, and E, coenzyme Q10, melatonin, ω-3/ω-6 fatty acids, and various natural compounds like coffee, green tea, bear bile, coleus, and tropical fruits, may help regulate intraocular pressure (IOP) and protect retinal neurons from oxidative and neural stress.[51]

Compared to rats given a regular diet, vitamin E deprivation in a rat glaucoma model caused higher lipid peroxidation, which in turn caused more retinal ganglion cell (RGC) mortality.[52]

Furthermore, some researchers have created a contact lens that contains additional vitamin E, proving that this method works well for administering antihypertensive combination medication (timolol + dorzolamide) through contact lenses.[53]

Stem Cell Treatment

Restoring vision lost due to glaucoma may be possible using stem cell treatment, which presents a fascinating opportunity to regenerate and replenish retinal ganglion cells (RGCs). Studies have shown that human embryonic stem cells can successfully differentiate into RGCs and integrate into the host retina, indicating that mesenchymal and human embryonic stem cells can be used for glaucoma neuroprotection. To fully achieve the potential of stem cell-based therapeutics for glaucoma, it still faces enormous ethical and scientific difficulties, despite the fact that multiple clinical trials are now underway.[54]

Mesenchymal stem cells (MSCs) may support the survival and endogenous healing of damaged retinal ganglion cells (RGCs) via a paracrine mechanism, according to multiple lines of evidence.

According to Harper et al., lentiviral-transduced MSCs that produce brain-derived neurotrophic factor (BDNF) can live in eyes with chronic hypertension, protecting the retina and optic nerve both structurally and functionally. According to this study, transplanting stem cells that produce BDNF may be a good way to treat glaucoma.[54]

DISCUSSION

Analysis and Discussion: Research into the neuroprotective potential of antiglaucoma therapy is promising, but there is still work to be done to turn this potential into practical treatments. The main cause of glaucoma, a major contributor to irreversible blindness, is elevated intraocular pressure (IOP), which harms retinal ganglion cells (RGCs). There is growing interest in directly safeguarding nerve cells, even though conventional treatments concentrate on decreasing IOP. The capacity of neuroprotective therapies to prevent or even reverse RGC damage is what gives them their real worth, but proving this requires complicated clinical trials that evaluate both nerve protection and IOP reduction. Some antiglaucoma drugs, such as α2-adrenergic agonists and β-blockers, may offer neuroprotective effects by influencing various cellular pathways, though strong clinical evidence for preventing long-term disease progression is still lacking.

Designing trials that accurately measure nerve protection is challenging, as traditional metrics like IOP reduction may not fully reflect nerve health. Identifying effective treatment combinations that lower IOP while also protecting nerves is crucial. Personalized medicine, which tailors treatments based on individual genetics, disease stage, and drug responses, is a key advancement. This approach aims to improve treatment effectiveness and minimize side effects, supported by progress in genetic research and biomarkers.

Stem cell research also presents promising opportunities for neuroprotection, with studies showing that stem cell-derived neurotrophic factors can protect and repair RGCs. However, translating these findings into real-world treatments requires overcoming safety, ethical, and procedural challenges. The variety of pharmacological and experimental approaches reflects the complexity of glaucoma. While traditional treatments focus mainly on IOP reduction, newer options like Rho kinase inhibitors and NMDA antagonists aim for direct nerve protection, each offering unique benefits.

CONCLUSION

Antiglaucoma medications lower intraocular pressure (IOP) and offer potential neuroprotective benefits, helping to preserve retinal ganglion cells (RGCs) and optic nerve integrity. Further research is needed to fully establish effects of neuroprotective agents.Recent studies emphasize the complex factors driving glaucomatous neurodegeneration, including biomechanical stress, vascular issues, aging, genetics, and neuroinflammation. Chronic inflammation in the retina and optic nerve damages neurons, with emerging therapies targeting neuroinflammation showing promise for protecting RGCs.

Immunomodulatory strategies could support RGC recovery by addressing multiple neurodegenerative pathways, particularly through the link between inflammation and mitochondrial dysfunction. Targeting inflammatory mediators may protect mitochondria and restore cellular metabolism, while

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mitochondrial restoration could also act as an immunomodulatory treatment.

In conclusion, targeting the intersection of neuroinflammation and mitochondrial function offers a promising direction for developing effective glaucoma therapies. Combining these approaches with current neuroprotective strategies and improving drug delivery could significantly enhance patient outcomes.

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