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Neuroprotection in glaucoma: a review of available methods

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HIGHLIGHTS

Neuroprotection in glaucoma represents a dynamically developing area, offering hope for more effective prevention of vision loss in the future.

ABSTRACT

Glaucoma is a progressive optic neuropathy that, if untreated, leads to irreversible blindness. It ranks second worldwide among causes of permanent vision loss. Although the primary goal of treatment is to lower intraocular pressure, increasing attention is being paid to neuroprotective strategies aimed at protecting retinal ganglion cells from degeneration. This paper aims to review the available methods of neuroprotection in glaucoma. Both pharmacological approaches, including Rho kinase inhibitors, glutamate antagonists (memantine, citicoline), adrenergic receptor agonists (brimonidine), statins, neurotrophic factors, antioxidants, cannabinoids, herbal preparations (*Ginkgo biloba*, huperzine A), and modern cell-based therapies are discussed. The mechanisms of action of these agents and the current status of clinical research are also included. Although many of these methods show promising results in experimental models, the clinical effectiveness of most interventions remains under investigation.

Key words: neuroprotection, glaucoma, Rho kinase inhibitors, brimonidine, memantine, citicoline, statins, calcium channel blockers, neurotrophic factors, cannabinoids, antioxidants, *Ginkgo biloba*, melatonin, huperzine A, stem cells

INTRODUCTION

Glaucoma is a group of optic nerve neuropathies. It leads to cupping of the optic nerve head and degeneration of retinal ganglion cells. It is ranked as the second leading cause of irreversible blindness worldwide and affects approximately 66.8% of the population [1]. An increase in intraocular pressure above 21 mmHg is considered a predisposing factor for the development of the disease. Three types of glaucoma are distinguished:

- primary (open-angle or angle-closure)
- secondary
- normal-tension glaucoma (up to 21 mmHg) – despite normal intraocular pressure, retinal cell degeneration occurs.

Studies conducted in Japan and Singapore have shown that there are unidentified factors contributing to disease development. Known risk factors include chronic ischemia, free radical formation, reactive oxygen species, and impaired axonal transport. Neurons have a limited capacity for regeneration; therefore, current research focuses on neuroprotective strategies aimed at preventing neuronal degeneration [1].

NEUROPROTECTION

Neuroprotection refers to supporting the regeneration and/or maintenance of neuronal viability after injury or degeneration. Reduction of intraocular pressure contributes to delaying retinal ganglion cell death and is sometimes regarded as a neuroprotective effect. However, in the context of glaucoma, neuroprotection is defined as any therapeutic intervention independent of intraocular pressure lowering that aims to protect retinal ganglion cells from degeneration [2]. Neuroprotective agents include Rho kinase inhibitors, α_2-adrenergic agonists (brimonidine), glutamate antagonists (memantine and citicoline), statins, calcium channel blockers, neurotrophic factors, cannabinoids, antioxidants, *Ginkgo biloba*, melatonin, huperzine A, and stem cells.

RHO KINASE INHIBITORS

Rho kinase inhibitors belong to a new class of hypotensive agents used in glaucoma treatment. These include ripasudil (approved in Japan in 2014) and netarsudil (approved in the United States in 2017) [3]. The mechanism of action of this drug class involves increasing aqueous humor outflow by inhibiting trabecular meshwork cell contraction, thereby lowering intraocular pressure. Rho kinase inhibitors also reduce scarring and fibroblast proliferation, supporting healing after glaucoma surgical procedures. Ripasudil effectively lowers intraocular pressure and enhances repair mechanisms [1].

A study evaluated its ability to promote axonal regeneration compared with other Rho kinase inhibitors. The results indicate that ripasudil prolongs retinal ganglion cell survival by suppressing oxidative stress. It was also confirmed that ripasudil does not act as a direct antioxidant, although the precise mechanism of action has not yet been fully elucidated. Furthermore, researchers found that the neuroprotective effects of ripasudil and fasudil were similar, but the specificity of ripasudil's effect was 2–18 times greater. Ripasudil has the potential to become a novel neuroprotective agent in glaucoma treatment; however, its effect is dose-dependent [3].

MEMANTINE AND CITICOLINE

Glutamate, as a neurotransmitter of the central nervous system, acts via NMDA and non-NMDA receptors and exerts pro-apoptotic effects. Its excess is considered a risk factor for glaucoma. The NMDA receptor antagonist memantine has neuroprotective properties; however, clinical trials have not confirmed its effectiveness in delaying visual field loss progression. Citicoline exhibits neuroprotective properties and counteracts glutamate toxicity. It reduces oxidative stress in retinal ganglion cells. As a precursor of acetylcholine, it supports cholinergic transmission, which is crucial for retinal ganglion cell survival. After crossing the blood–brain barrier, citicoline participates in the synthesis of phosphatidylcholine, acetylcholine, sphingomyelin, and cardiolipin, supporting both neurotransmission and the repair of cell membranes. Its role in maintaining normal sphingomyelin levels has also been demonstrated, which translates into improved axonal function and survival of retinal ganglion cells. Citicoline therapy delays degenerative changes; however, its effects are transient and therefore require continuous administration [4]. Studies have shown that citicoline, vitamin B_3, and coenzyme Q10 exert beneficial effects on neurons exposed to oxidative stress, with the greatest efficacy observed for their fixed combination. By influencing mitochondrial function, these substances may act synergistically, which is particularly relevant in the pathogenesis of neurodegenerative diseases. Moreover, their ability to reduce inflammatory marker levels and increase neurotrophin expression indicates potential neuroprotective properties. Given the multifactorial nature of most neurodegenerative diseases, combined use of citicoline, vitamin B_3, and coenzyme Q10 may represent a promising therapeutic approach. Confirmation of these findings in clinical trials could open new avenues for the treatment of vision-threatening diseases such as glaucoma and diabetic retinopathy [5–8].

BRIMONIDINE

Brimonidine activates α_2-adrenergic receptors, resulting in reduced aqueous humor production and increased outflow. Consequently, it lowers intraocular pressure and prevents glaucoma progression. It is one of the main classes of topical ocular hypotensive agents [4].

The drug also blocks NMDA receptors and reduces glutamate accumulation, thereby exerting a protective effect. Preclinical studies have confirmed the neuroprotective influence of brimonidine, which led to the development of an implant containing this substance. Its effectiveness is currently being investigated in patients with glaucomatous optic neuropathy [5].

STATINS

Statins, used in the treatment of hypercholesterolemia, inhibit the enzyme HMG-CoA reductase, thereby reducing cholesterol synthesis. They also exhibit anti-inflammatory effects through inhibition of Rho kinase. In addition to influencing the cytoskeleton of trabecular meshwork and ciliary body cells in vitro, they also protect astrocytes of the optic nerve head. Their ability to inhibit transforming growth factor β_2 (TGF-β_2), a factor involved in extracellular matrix remodeling, is of neuroprotective significance in glaucoma [4].

NEUROTROPHIC FACTORS

Neurotrophic factors support neuronal development and survival by acting on tropomyosin receptors and the p75 neurotrophin receptor (p75NTR). In glaucoma, they promote the survival of retinal ganglion cells through activation of the Erk1/2 and c-Jun signaling pathways and inhibition of caspase-2.

Brain-derived neurotrophic factor (BDNF), produced locally by retinal ganglion cells and the brain, is transported to the retina via retrograde axonal transport. Exogenous administration of neurotrophic factors may provide temporary cellular protection; however, therapeutic efficacy is limited by a decrease in TrkB receptor expression. Better outcomes have been observed with intravitreal administration of combinations of neurotrophic factors, such as ciliary and glial factors. Nevertheless, the precise mechanisms of action and axonal transport of these substances are not yet fully understood, which limits the effectiveness of therapies based on their supplementation [4].

ANTIOXIDANTS

Reactive oxygen species activate glial cells, leading to damage of the optic nerve head. In glaucoma models, the use of antioxidants such as tempol reduces inflammation and neurodegeneration by inhibiting the activity of the nuclear transcription factor κB (NF-κB) in retinal ganglion cells (RGCs). Resveratrol, an activator of sirtuin-1, exhibits strong antioxidant properties. In animal models, its intravitreal or intraperitoneal administration inhibits oxidative stress and RGC apoptosis while increasing BDNF expression and suppressing pro-apoptotic proteins [4]. Coenzyme Q10 plays an important role in ATP production and has strong antioxidant properties, thereby protecting cells from oxidative stress. In in vitro studies, coenzyme Q10 inhibited oxidative stress-induced activation of optic nerve astrocytes, reduced the expression of cellular stress markers (SOD2, HO-1), and prevented mitochondrial damage. In animal models, both topical and systemic administration of coenzyme Q10 protected RGCs from apoptosis by stabilizing mitochondrial function and reducing glutamate toxicity. Its efficacy was also confirmed in experimental glaucoma models, where coenzyme Q10 improved RGC survival and limited glial cell activation. In patients with glaucoma, topical administration of coenzyme Q10 combined with vitamin E significantly improved visual evoked potential (VEP) outcomes. The bioavailability of coenzyme Q10 remains variable and depends on the formulation; achieving a therapeutic effect requires maintaining high plasma concentrations, which can be accomplished through appropriate supplementation and the use of modern formulations such as sustained-release systems [7]. To assess the impact of oxidative stress on glaucoma development, mice were fed an α-lipoic acid-enriched diet using two regimens: an interventional approach (starting at 6 months of age) and a preventive approach. After 4 and 11 months of supplementation (at 10 and 12 months of age), the expression of antioxidant genes and proteins, the number of retinal ganglion cells, axonal transport, and axonal integrity were analyzed. In both models, α-lipoic acid enhanced the expression of protective mechanisms, preserved retinal ganglion cells, improved retrograde transport, and reduced oxidative stress, confirming its effectiveness as a dietary intervention for protection against glaucoma [9, 10].

STEM CELLS

Stem cell therapy represents a promising approach in the treatment of glaucoma. It enables cellular regeneration and creates a supportive environment for cell survival. Animal models have confirmed the effectiveness of mesenchymal cells in protecting retinal ganglion cells. Human embryonic stem cells, due to their pluripotency, may serve as a source of retinal ganglion cells; however, their use raises ethical and scientific concerns [11–14]. Mesenchymal stem cells can differentiate into retinal ganglion cell–like cells, secrete neurotrophins (including BDNF, CNTF – ciliary neurotrophic factor, NGF – nerve growth factor, and PDGF

– platelet-derived growth factor), and release exosomes – carriers of proteins that support neuronal survival. Studies have demonstrated the effectiveness of genetically modified stem cells engineered to overexpress BDNF and NGF [4]. Other sources, such as neural progenitor cells, retinal stem cells, and induced pluripotent stem cells, also exhibit neuroprotective potential. Despite promising results, the safety of stem cell therapy remains a concern due to the risk of tumor formation and adverse effects such as inflammation or gliosis. Ongoing research focuses on improving safety and efficacy, as well as enhancing the integration of transplanted cells with the retina and the brain [15].

CANNABINOIDS

Cannabinoid and glutamatergic signaling systems interact and cooperate within the retina. In glaucoma, an excess of glutamate in the retinal ganglion cell layer may lead to ganglion cell death. In a mouse study, administration of a CB1/CB2 cannabinoid receptor agonist (WIN 55,212-2) significantly improved retinal ganglion cell survival after NMDA-induced injury. These results suggest that cannabinoids may exert a neuroprotective role in neurodegenerative diseases such as glaucoma [6].

GINKGO BILOBA

Ginkgo biloba is a traditionally used medicinal agent whose extract has attracted interest as a potential neuroprotective factor in glaucoma therapy. It is suggested that its effects may result from improved blood flow through mechanisms such as reduced blood viscosity and inhibition of platelet activation, as well as from antioxidant properties related to the presence of flavonoids, which limit oxidative stress at the mitochondrial level. However, clinical studies conducted to date have produced inconclusive results. Some of them indicate improvement in visual field parameters after supplementation with *Ginkgo biloba* preparations in patients with normal-tension glaucoma, independent of any effect on intraocular pressure, whereas other studies have not confirmed such an effect. These discrepancies may result from differences in treatment regimens, duration of follow-up, and characteristics of the studied populations. Preliminary observations also suggest a possible effect of the substance on improving peripapillary vessel density, which may be relevant in slowing disease progression. To definitively assess the effectiveness of *Ginkgo biloba* extract in glaucoma therapy, further clinical studies are required [9].

HUPERZINE A

Huperzine A is a plant-derived compound obtained from *Huperzia serrata*, which grows in China. It acts as a reversible acetylcholinesterase inhibitor, increasing acetylcholine levels. It is used in the treatment of Alzheimer's disease, where it improves memory function. Studies have shown that it reduces β-amyloid production in the brain. In addition, it improves cognitive function in patients with chronic cerebral ischemia through activation of nicotinic acetylcholine receptors. A study was conducted to evaluate the role and mechanisms of huperzine A in lowering intraocular pressure and providing retinal neuroprotection. The analysis demonstrated a dual effect of huperzine A, consisting of reduction of intraocular pressure and retinal neuroprotection. Huperzine A (0.01%) was as effective as 2% pilocarpine in inducing pupil constriction. Moreover, it exhibited neuroprotective effects by increasing neuronal cell survival, reducing oxidative stress, and reversing apoptosis. The neuroprotective action of huperzine A may result from inhibition of acetylcholinesterase, leading to increased acetylcholine levels and activation of the muscarinic acetylcholine receptor M1. Further studies are necessary to fully understand its mechanisms of action in the treatment and neuroprotection of glaucoma [11].

MELATONIN

Melatonin, produced not only in the pineal gland but also in ocular structures, plays a key role in the regulation of intraocular pressure. Glaucoma is a leading cause of vision loss. Although drugs that lower intraocular pressure are available, the search for safer therapies continues. Melatonin and its analogues effectively reduce intraocular pressure in both normotensive conditions and ocular hypertension [14]. Studies indicate that in patients with glaucoma, the level of 6-sulfatoxymelatonin (the main metabolite of melatonin) is significantly reduced, suggesting disturbances in circadian rhythm that melatonin may help normalize. In an NMDA-induced retinal injury model, melatonin was found to effectively protect retinal ganglion cells from glutamate-induced excitotoxicity. A melatonin concentration of 400 μM provided complete protection of R28 cells, and even higher doses were not toxic. Treatment also improved visual function in mice, as confirmed by flash visual evoked potential (FVEP) studies. As a potent antioxidant, melatonin scavenges free radicals, protecting cells from oxidative stress. However, under excitotoxic conditions, glutathione levels did not increase, suggesting that melatonin acts through mechanisms beyond antioxidative pathways alone. Retinal RNA sequencing showed that melatonin corrects NMDA-induced dysregulation of gene expression, thereby effectively protecting retinal ganglion cells. It also supports visual function and reduces oxidative stress. These effects may be associated with activation of the PI3K–AKT and JAK–STAT signaling pathways, although further studies are required to fully elucidate the underlying mechanisms [13].

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are used in the treatment of hypertension. They increase blood flow and lower blood pressure by inhibiting calcium influx into smooth muscle cells. Studies have demonstrated their effectiveness in slowing visual field progression in normal-tension glaucoma (including nifedipine, brovincamine, diltiazem, verapamil, and nilvadipine). These drugs improve blood flow in the optic nerve and choroid and reduce optic nerve damage.
Nilvadipine, due to its high lipophilicity and ability to accumulate in the retina, is considered particularly promising in glaucoma therapy, although the mechanism of its neuroprotective action has not yet been fully elucidated. In a mouse model of ocular hypertension, its neuroprotective effects on retinal ganglion cells were investigated. Ocular hypertension was induced by laser treatment in one eye, followed by administration of nilvadipine or a vehicle for 8 weeks. The increase in intraocular pressure was similar in both groups; however, nilvadipine significantly limited retinal ganglion cell loss compared with the control group. In the vehicle-treated group, retinal ganglion cell survival was closely correlated with the magnitude of pressure-induced injury, a relationship not observed with nilvadipine. These results suggest that nilvadipine may have a significant neuroprotective effect in glaucoma [16].

CONCLUSION

Glaucoma, the second most common cause of irreversible blindness, is characterized by progressive loss of retinal ganglion cells. In addition to elevated intraocular pressure, oxidative stress, ischemia, and disturbances in axonal transport contribute to its pathogenesis. Due to the limited regenerative capacity of neurons, increasing importance is being placed on neuroprotection in the prevention of the disease. Although the results of preclinical studies are promising, the effectiveness of many methods has not been confirmed in clinical trials, indicating the need for further research into effective neuroprotection in glaucoma.

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