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Neuroprotection in glaucoma – what is the role of brimonidine?

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HIGHLIGHTS

Studies have shown that 0.2% brimonidine protects retinal ganglion cells from apoptosis, not only in the mechanism of lowering intraocular pressure.

ABSTRACT

Glaucoma is a chronic, multifactorial, progressive optic neuropathy and if left untreated, leads to total blindness. Damage to retinal ganglion cells and their axons in glaucoma may be caused by increased intraocular pressure, ischemia, oxidative stress, glutamate neurotoxicity, or deficiency of neurotrophic growth factor. Brimonidine is an α_2-adrenergic receptor agonist, a drug commonly used to lower intraocular pressure. Its action is to inhibit the production of aqueous humor and increase its outflow by an unconventional (uveoscleral) route. The neuroprotective mechanism of action of brimonidine is believed to be related to the reduction of extracellular glutamate and blocking the activation of N-methyl-D-aspartate (NMDA) receptors, as well as the activation of brain-derived neurotrophic factor (BDNF protein) and fibroblast growth factor and their receptors, vascular modulation improving microcirculation, and regulation of cell survival and apoptosis signals. Studies have shown that 0.2% brimonidine protects retinal ganglion cells from death, not only in the mechanism of lowering IOP. The use of neuroprotective treatment of retinal ganglion cells is a promising route in glaucoma therapy.

Key words: glaucoma, neuroprotection, brimonidine

INTRODUCTION

Glaucoma is a chronic, progressive, and multifactorial optic neuropathy that, if left untreated, can ultimately lead to irreversible blindness. It is characterized by the degeneration of retinal ganglion cells and corresponding visual field loss. Damage to retinal ganglion cells (RGCs) and their axons in glaucoma is multifactorial, with elevated intraocular pressure (IOP) being the predominant factor. Increased IOP leads to deformation of the lamina cribrosa and impaired axoplasmic flow. Additional mechanisms contributing to RGC injury include ischemia, oxidative stress, glutamate excitotoxicity, and neurotrophic factor deficiency.

THE ROLE OF INTRAOCULAR PRESSURE

Although IOP remains the only established and modifiable risk factor for glaucoma, its reduction, even when combined with the elimination of diurnal fluctuations, does not always prevent disease progression. This observation indicates that non-IOP-dependent mechanisms also play a crucial role in the pathogenesis of glaucoma [1]. This concept is supported by the findings of the Ocular Hypertension Treatment Study, in which no progression of glaucoma was observed despite an IOP as high as 32 mmHg, and the Collaborative Normal-Tension Glaucoma Study, which demonstrated ongoing neurodegeneration in patients with IOP values below 21 mmHg [2, 3]. Factors such as apoptotic mediators, oxidative stress, ischemic changes, impaired ocular blood flow, and neurotoxins are believed to play a significant role in the pathogenesis of glaucoma [4].

NEUROPROTECTION

For this reason, increasing attention in glaucoma therapy has turned toward neuroprotection, a strategy aimed at halting or delaying glaucomatous neurodegeneration independently of IOP control. Doozandeh and Yazdani define neuroprotection as any intervention, beyond IOP reduction, that prevents the death of retinal ganglion cells [5]. Neuroprotective agents act by reducing neuronal loss, thereby enhancing the survival and functional capacity of retinal ganglion cells and supporting long-term visual function [6].

NEUROPROTECTIVE EFFECTS OF BRIMONIDINE

Brimonidine is an α_2-adrenergic receptor agonist widely used in glaucoma therapy to reduce IOP. Its mechanism of action involves both suppression of aqueous humor production and enhancement of uveoscleral (nonconventional) outflow. Beyond its hypotensive effect, growing evidence supports a direct neuroprotective role of brimonidine in glaucoma [7]. Notably, the U.S. Food and Drug Administration (FDA) classifies brimonidine as pregnancy category B, which makes it a particularly relevant therapeutic option for managing glaucoma in pregnant patients. However, brimonidine use is contraindicated in the third trimester of pregnancy due to the risk of fetal central nervous system depression. It is also not recommended during breastfeeding and is contraindicated in children under 5 years of age; in those aged 5–10 years, it should be prescribed with extreme caution. Compared with another selective α_2-adrenergic agonist, apraclonidine, brimonidine is associated with a markedly lower incidence of topical allergic reactions [8].

The neuroprotective mechanism of brimonidine is thought to involve several pathways, including the reduction of extracellular glutamate and inhibition of N-methyl-D-aspartate (NMDA) receptor activation. In addition, brimonidine promotes the activation of brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF) signaling pathways, exerts vascular modulation that enhances ocular microcirculation, and regulates cell survival and apoptosis signaling [5, 7, 9]. In addition, brimonidine exhibits anti-cytotoxic properties by promoting neuronal regeneration and survival following injury caused by ischemia, NMDA-induced neurotoxicity, ocular hypertension, optic nerve crush, or inflammation. These effects are partly mediated through the reduction of glutamate accumulation, among other mechanisms [7, 9–11].

The neuroprotective effect of brimonidine is primarily aimed at counteracting neurotoxicity induced by excessive glutamate synthesis, reactive oxygen species, nitric oxide, calcium channel overactivation, and vascular insufficiency, all of which contribute to apoptosis of retinal ganglion cells. Studies in animal models have demonstrated that brimonidine increases the survival of retinal ganglion cells independently of its IOP-lowering effect, thereby fulfilling the definition of neuroprotection [12, 13]. However, in clinical settings, it is difficult to isolate this effect, since brimonidine also reduces IOP and may inhibit glaucomatous neuropathy through pressure-lowering mechanisms. In a study by Mohamed et al., which evaluated the effect of brimonidine on visual field parameters in 16 patients with primary open-angle glaucoma and medically controlled IOP, the addition of brimonidine 0.2% not only further reduced baseline IOP but also improved visual field scores [14]. However, it remains unclear whether the observed visual field improvement was due to a true IOP-independent neuroprotective effect or simply the result of additional IOP reduction. In contrast, the Low-pressure Glaucoma Treatment Study (LoGTS) directly assessed the potential neuroprotective effect of brimonidine by comparing it with timolol in patients with normal-tension glaucoma. This multicenter, double-blind, randomized trial enrolled 99 patients treated with 0.2% brimonidine and 79 patients treated with 0.5% timolol. Despite

achieving similar IOP reductions in both groups, the incidence of visual field progression was significantly lower in the brimonidine group compared with the timolol group (9.1% vs. 39.2%) [15]. A similar comparison of the same anti-glaucoma agents in ocular hypertension was conducted by Tsai et al. [16]. In this study, treatment with 0.2% brimonidine resulted in a statistically significant reduction in retinal nerve fiber layer (RNFL) loss compared with 0.5% timolol, independent of the IOP-lowering effect.

It should be emphasized that the neuroprotective effect of 0.2% brimonidine, administered as ophthalmic drops into the conjunctival sac, depends on achieving an adequate concentration in the vitreous body. A study by Kent et al. demonstrated that topically applied brimonidine can reach concentrations sufficient to activate α_2-adrenergic receptors in the vitreous. Interestingly, patients with aphakia or pseudophakia exhibited higher vitreous drug concentrations compared with those retaining their natural lens [17].

OTHER SUBSTANCES WITH NEUROPROTECTIVE POTENTIAL

Since neuroprotective strategies have already been approved in neurological diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis – where the mechanisms of neuronal death resemble those observed in glaucomatous neuropathy — the concept of neuroprotection in glaucoma holds considerable therapeutic potential. Potentially neuroprotective agents in glaucoma therapy, with either direct or indirect effects, include β-blockers, prostaglandin analogs, carbonic anhydrase inhibitors, Rho kinase inhibitors, NMDA receptor antagonists (e.g., memantine), calcium channel blockers, citicoline, nicotinamide, antioxidants, Ginkgo biloba extract, melatonin, saffron extract, as well as emerging approaches such as gene therapy, exosomes, stem cell therapy, and neurotrophins [7].

CONCLUSIONS

Brimonidine is one of the few anti-glaucoma agents shown to exert a neuroprotective effect in addition to lowering IOP. This dual mechanism may be particularly advantageous in patients with progressive glaucomatous neuropathy despite normal IOP. Evidence indicates that brimonidine 0.2% protects retinal ganglion cells through pathways beyond IOP reduction, supporting its role as both an IOP-lowering and neuroprotective therapy. Thanks to its dual mechanism of lowering IOP and providing neuroprotection, brimonidine may play an important role in glaucoma management, particularly in patients where adding a second agent could compromise compliance. It can also serve as a valuable adjunctive therapy. The concept of protecting retinal ganglion cells through neuroprotective strategies represents a promising direction in the future of glaucoma treatment.

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References

1. Leske MC, Heijl A, Hussein M et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003; 121(1): 48-56.
2. Kass MA, Heuer DK, Higginbotham EJ et al. The Ocular Hypertension Treatment Study: A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002; 120: 701-13. http://doi.org/10.1001/archopht.120.6.701.
3. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. Am J Ophthalmol. 1998; 126: 487-97. http://doi.org/10.1016/s0002-9394(98)00223-2.
4. Vishwaraj CR, Kavitha S, Venkatesh R et al. Neuroprotection in glaucoma. Indian J Ophthalmol. 2022; 70(2): 380-5. http://doi.org/10.4103/ijo.IJO_1158_21.

5. Doozandeh A, Yazdani S. Neuroprotection in Glaucoma. J Ophthalmic Vis Res. 2016; 11(2): 209-20. http://doi.org/10.4103/2008-322X.183923.
6. Weinreb RN, Levin LA. Is neuroprotection a viable therapy for glaucoma? Arch Ophthalmol. 1999; 117(11): 1540-4. http://doi.org/10.1001/archopht.117.11.1540.
7. Asanad S, Chang J, Aref AA. et al. Neuroprotection in Glaucoma. https://eyewiki.org/Neuroprotection_in_Glaucoma.
8. Basic and Clinical Science Course, Section 10: Glaucoma. 2024-2025 edition.
9. Donello J, Padillo E, Webster M et al. α2-Adrenoceptor Agonists Inhibit Vitreal Glutamate and Aspartate Accumulation and Preserve Retinal Function after Transient Ischemia. J Pharmacol Exp Ther. 2001; 296(1): 216-23.
10. Wheeler L, Woldemussie E, Lai R. Role of Alpha-2 Agonists in Neuroprotection. Survey Ophthal. 2003; 48: S47-51.
11. Lai R, Chun T, Hasson D et al. Alpha-2 adrenoceptor agonist protects retinal function after acute retinal ischemic injury in the rat. Vis Neurosci. 2002; 19: 175-85.
12. Hernández M, Urcola JH, Vecino E. Retinal ganglion cell neuroprotection in a rat model of glaucoma following brimonidine, latanoprost or combined treatments. Exp Eye Res. 2008; 86(5): 798-806.
13. Woldemussie E, Ruiz G, Wijono M et al. Neuroprotection of retinal ganglion cells by brimonidine in rats with laser-induced chronic ocular hypertension. Invest Ophthalmol Vis Sci. 2001; 42: 2849-55.
14. Mohamed J, Abo-Elkhei O. The Role of Brimonidine Eye Drops as an Adjunctive Therapy for Optic Nerve Protection in Patients with Controlled Open Angle Glaucoma. Egypt J Hosp Med. 2017; 68(3): 1418-24.
15. Krupin T, Liebmann J, Greenfield D et al. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. Am J Ophthalmol. 2011; 151(4): 671-81.
16. Tsai J-C, Chang H-W. Comparison of the effects of brimonidine 0.2% and timolol 0.5% on retinal nerve fiber layer thickness in ocular hypertensive patients: a prospective, unmasked study. J Ocul Pharmacol Ther. 2005; 21: 475-82.
17. Kent A, Nussdorf J, David R et al. Vitreous concentration of topically applied brimonidine tartrate 0.2%. Ophthalmology. 2001; 108(4): 784-7.

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