Secondary neuroprotective effects of hypotensive drugs and potential mechanisms of action

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Abstract

Primary open-angle glaucoma, a long-term degenerative ocular neuropathy, remains a significant cause of vision impairment worldwide. While many risk factors have been correlated with increased risk for primary open-angle glaucoma, intraocular pressure (IOP) remains the only modifiable risk factor and primary therapeutic target. Pharmacologic therapies are administered topically; these include α_2-agonists, β-antagonists, prostaglandin analogs and carbonic anhydrase inhibitors. Some of these topical medications exhibit secondary neuroprotective effects independent of their effect on IOP. This review covers the possible mechanisms of neuroprotection stimulated by drugs currently marketed for the lowering of IOP, based on known literature. While the neuroprotective properties of many glaucoma pharmaceuticals are promising from an experimental standpoint, key challenges for the development of new clinical practices include unknown systemic side effects, limited methods of drug delivery to the retina and optic nerve, and development of extended-release formulations.

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Keywords

Glaucoma, a leading cause of blindness worldwide, is a long-term degenerative ocular neuropathy resulting in retinal ganglion cell (RGC) dysfunction and corresponding loss to the visual field. It is estimated that over 60 million individuals were afflicted with open-angle and angle-closure glaucoma as of 2010, which will increase to almost 80 million by 2020 [1]. The disease affects all ethnicities, and 6.7 million people are bilaterally blind as a result [1]. The most common type of glaucoma is primary open-angle glaucoma (POAG), which presents clinically with increased cupping of the optic disk and associated field deficits, although the anterior chamber angle remains open and additional acute factors, such inflammation or trauma, are absent.

Various risk factors are associated with the development of glaucoma, including several comorbidities. The most prominent primary risk factors are of course age, intraocular pressure (IOP) and ethnicity. A meta-analysis of recent population-based studies in the USA, Australia and Europe found that subjects of African descent had almost three-times the prevalence of POAG compared with Caucasians [2]. The age-adjusted rate of blindness from glaucoma is 6.6-fold higher than that among Caucasians and blindness begins an average of 10 years earlier [3]. However, in older age groups, the prevalence of POAG in Latin American and Chinese populations approached that of African-descent individuals [1].

Despite the diversity of risk factors associated with glaucoma, IOP is currently the only modifiable risk factor and therefore the main target for therapeutic interventions. However, glaucomatous progression has been estimated to continue in as many as half of glaucoma patients undergoing an IOP-lowering regimen [4]. While controversial and highly variable across studies, such estimates support the growing consensus that pathophysiologic factors aside from IOP may play an important role in the progression of vision loss in glaucoma. For this reason, over the past decade in particular, medications currently on the market to lower IOP in glaucoma have been the subject of investigations to reveal secondary neuroprotective properties. The nature of these medications and the possible mechanisms underlying their putative neuroprotective effects will be the focus of this review.

Glaucoma & IOP

A long and detailed history embedded deeply in the literature supports a strong association between IOP and the development and progression of POAG [5–8]. Results from the Early Manifest Glaucoma Trial indicated that for patients diagnosed with POAG, mean IOP was a significant risk factor for glaucoma progression over an average of 8 years, even when IOP was within the 'normal' range of 8–22 mmHg [9]. Additionally, lowering IOP with topical drugs in patients with elevated IOP but without demonstrable visual field defects can delay or prevent disease onset [10]. From a structural standpoint, the use of IOP-lowering medication also reduces the risk of both optic disc deterioration and changes in visual field performance [11].

The relationship between IOP and glaucoma is complex. Despite popular simplifications, POAG is not synonymous with elevated IOP. Approximately 15–25% of individuals with open-angle glaucoma are classified as normotensive based on IOP measurements, and 33–50% of individuals with changes in optic disc appearance and visual field deficits demonstrate IOP within the normal range [12–14]. These patients have been placed in a subgroup commonly referred to as 'low-tension' or 'normal-tension' glaucoma. It is

noteworthy, however, that the Baltimore Eye Study concluded that such a distinction is artificial and probably does not represent discrete etiological subgroups [15]. Across the board, glaucomatous pathology without elevated IOP has been estimated at representing roughly half of all diagnoses [16]. The majority of patients diagnosed with POAG in Asia have IOPs in the normal-tension range [8]. By contrast, many patients with consistently elevated IOP never develop characteristic glaucomatous optic disk appearance or deficits in visual fields [6,11].

For the reasons outlined above, although elevated IOP and glaucoma are clearly associated, elevations beyond what is considered the normal IOP range are neither necessary nor sufficient for diagnosis. Even so, IOP-lowering topical medications are still the standard of treatment for all patients, even those classified as normal tension. This is certainly justified. The Collaborative Normal-Tension Glaucoma Study found a slower rate of incident visual field loss in cases with a 30% or more decrease in IOP [17]. It is important to note that even in this study, 20% of eyes continued with progression to glaucomatous changes, even when IOP was reduced 30% or more from baseline. This highlights the need for newer therapies that directly target the neural substrates for vision loss in glaucoma. Based on the evidence, it would make sense to begin with common topical hypotensives (Box 1), especially should further investigation support secondary actions directly modulating pathogenic mechanisms at the neural level.

Progression of neurodegeneration in glaucoma

Glaucoma is most frequently diagnosed by assessment of the optic disc and retinal nerve fiber layer, with concurrent monitoring of IOP and assessment of the visual field. While the full extent of pathophysiology across the disease spectrum is not completely understood, the various forms of glaucoma are categorically optic neuropathies and therefore are shared as a substrate for vision loss degeneration of the RGC projection to the brain. Loss of tissue in the retina, especially RGC axons, results in the distinct appearance of the optic disk and has been linked to concomitant visual field loss [18]. The assessment of correlations between RGC loss in the retina, deficits in visual sensitivity and retinal nerve fiber layer thickness are an active area of research, with much quantitative progress arising from experimental models using nonhuman primates [19,20].

The RGC projection to the brain is extensive, stretching many centimeters along the optic nerve between the posterior globe and central targets. It makes sense that an early and persistent focus on dissecting pathogenic mechanisms has been damage to the RGC axons, both proximal to the globe and at distal sites in the brain. Deficits in functional axonal transport have been described since the mid-1970s [21–23], and more recent investigations have described possible pathogenic mechanisms at the optic nerve head (ONH) as damaging normal axoplasmic flow [24–26]. ONH injury is thought to reduce retrograde transport of prosurvival factors such as BDNF from the RGC synaptic terminal in the brain to the cell body, thus triggering downstream apoptotic cascades [27,28]. However, in animal models of glaucoma, impaired anterograde axonal transport first becomes apparent in the RGC projection in the brain, far distal to the ONH, with progression working backwards towards the retina [29]. Therefore, mechanisms both at the ONH or elsewhere in the projection may transduce stress signals within the axons and inhibit transport more globally.

More and more evidence indicates that axonal injury is early in glaucoma and probably manifests as deficits in axonal transport [30]. While the progression of neurodegenerative events ultimately results in mitochondrial-mediated, caspase-dependent RGC apoptosis [31–36], there is growing movement away from viewing apoptosis as the direct cause of clinical presentation. Increasing support for the compartmentalization of neuronal degeneration

suggests that RGC neuronal processes are affected separately from the cell bodies, and may actually precede cell body loss [29,37–41]. For instance, deletion of the proapoptotic gene *BAX* in the DBA/2J mouse model of pigmentary glaucoma demonstrates a protective effect on the RGC body, but does not prevent optic nerve degeneration [42]. In addition, distal structures in the optic projection structure persist, even after the loss of axonal transport [29,40]. The persistence of the RGC soma following the loss of axonal transport and the axon itself may suggest a 'dying back' progression as part of glaucomatous neurodegeneration – a progressive distal-to-proximal cascade that begins at the synaptic terminals [43]. However, it seems likely that even this axonal injury may progress from critical pathogenic events at the ONH, which are transduced along the axon.

Targets for neuroprotection in glaucoma

Since the neuroretina develops as an evagination of the CNS, glaucoma shares a number of mechanistic elements with other neurodegenerative disorders of the CNS. Indeed, a diverse array of recent publications suggests numerous commonalities between glaucoma and CNS disorders. While disorders such as Alzheimer's, Parkinson's, amyotrophic lateral sclerosis and Huntington's disease result from diverse etiologies, their progression involves many common elements that may serve as targets for potential therapeutic interventions. Neurodegeneration in glaucoma shares many such common pathway components, and indicates that they hold promise as therapeutic targets [40,44–46].

Regarding glaucoma as a neurodegenerative disease introduces the possibility that neuroprotective strategies might be an efficacious means to slow or even stop degenerative progression entirely. Two definitions of neuroprotective agents prevail in the existing literature. The first is obvious: agents that indirectly counteract RGC degeneration by reducing eye-related stress, for example by reducing IOP. The second is far more intriguing from the standpoint of understanding mechanisms of progression: substances that slow degeneration through direct effects on components of the optic projection. Practically speaking, neuroprotective agents that conform to the latter definition must directly reach the retina and/or optic nerve and act upon cellular elements therein, such as medications that stimulate glial cells to produce insult-nullifying or other trophic factors (Box 2).

Cascades that contribute to RGC degeneration in glaucoma are as complex as they are diverse [30,46]. Equally diverse, then, are potential targets for neuroprotective drug therapies, including mitochondrial dysfunction, protein misfolding, oxidative stress, inflammatory mediators and neurotrophin signaling. Additionally, the ONH is an early site for changes in glial reactivity [47], which generates an inflammatory milieu for neighboring RGCs and supporting cell types [48–51]. Other evidence implicates a particular form of ischemic insult that triggers glutamate-induced, NMDA receptor-mediated excitotoxicity [52–55]. Several studies have suggested the involvement of reduced ocular blood flow in the pathogenesis of POAG [56–59], with one demonstrating up to a 24% reduction in blood flow through the optic nerve [60]. Ischemic reperfusion injury due to compromised circulation is believed to be one of the primary initiators of RGC death, and may be among the earliest events associated with RGC loss [31,61]. For this reason, it is essential to understand the effects of current IOP-lowering medications not only on RGCs and their axons, but also on elements of the retinal and optic nerve vasculature. Unfortunately, validating changes in ONH blood flow is difficult, and there is no way to separate primary effects from secondary effects that could be due to tissue loss.

α₂-adrenergic agonists

The α_2-adrenergic agonists include well-known topical medications such as brimonidine and apraclonidine. These lower IOP by decreasing aqueous humor production through

inhibition of adenylate cyclase inhibition, thus lowering cAMP levels [62]. The drugs also increase uveoscleral outflow [63]. Work in animal models has demonstrated α_{2A}-receptors in nonpigmented ciliary epithelium and in corneal conjunctival epithelia of the anterior segment and throughout cell bodies of the retina in the posterior segment [64]. Additionally, α_{2B}-receptors localize in neuronal dendrites and axons as well as glia, while α_{2C}-receptors localize in photoreceptor cell bodies and inner segments [64]. Similarly, in human cadaveric eyes, α_2-agonist sites have been identified primarily in iris epithelium and ciliary epithelium. Additional binding sites have also been localized to the ciliary muscle, retina, retinal pigment epithelium and choroid [65].

The α_2-agonists have been well marketed as glaucoma medications, and there has been long-held interest in their secondary neuroprotective effects. Many studies have documented enhancement of RGC cell body survival and of axonal function across a variety of acute models utilizing both ocular hypertension and other optic nerve injuries with systemic application of α-agonists [66–68]. These are reviewed in a recent study that found that systemic application of brimonidine prevented early axonopathy, including deficits in anterograde transport to the brain, and ensuing optic nerve and retinal degeneration with prolonged ocular hypertension [69]. A 2009 literature review of 48 articles addressing whether brimonidine met the criteria of neuroprotection found that it met all but the final neuroprotective criterion of success in humans [70].

The mechanisms of secondary neuroprotective effects afforded by the α-agonists have been more difficult to pinpoint and probably involve multiple pathways. Brimonidine appears to upregulate the expression of endogenous BDNF in rat RGCs [71]. BDNF has long been recognized for supporting the survival of existing neurons and encouraging the growth and differentiation of new neurites and synapses. Brimonidine also is linked to the upregulation in the retina of several additional prosurvival factors. These include the vascular basement membrane protein bFGF, the anti-apoptotic factors Bcl-2 and Bcl-xl, and the extracellular signal-regulated kinases (ERKs) and PI3K/Akt pathways [72,73]. Pretreatment of RGCs with brimonidine also resulted in significantly reduced NMDA-elicited whole-cell currents and cytosolic apoptotic calcium signals in RGCs [74], suggesting a mechanism of neuroprotection via RGC NMDA receptors (Figure 1).

Whatever the mechanisms that mediate neuroprotective properties for the α-agonists, they probably do not primarily involve increasing choroidal and optic nerve vascular flow. Topical α_2-agonists cause potent vasoconstriction and increased vascular resistance in choroidal vessels [75]. Brimonidine and other α_2-agonists have also been implicated as vasoconstrictors that can affect systemic blood pressure [76].

β-blockers

Topical β-adrenoreceptor blockers are one of the most commonly prescribed hypotensive medications for glaucoma. Their hypotensive effect is primarily mediated by the decrease of aqueous fluid with antagonism of β-adrenoreceptors in the anterior chamber of the eye [77,78]. Multiple studies have demonstrated evidence for a secondary neuroprotective effect of this class of drugs. Topical application of betaxolol, a selective β_1-receptor antagonist, attenuated thinning of the inner plexiform layer and loss of immunoreactivity for choline acetyltransferase following ischemic–reperfusion injury, the implication being rescue of synaptic connections [79]. Timolol, a more commonly prescribed nonselective β-blocker, exhibited protective effects on RGCs in a rat experimental glaucoma model [80]. The drug was found to reduce cell loss in the ganglion cell layer and to rescue a- and b-waves in the electroretinogram following both glutamate-induced excitotoxic insult and ischemic–reperfusion injury [81].

The β-blockers are likely to exert a secondary neuroprotective effect primarily via regulation of sodium and calcium channels, which are linked to the release of glutamate and subsequent activation of NMDA receptors (Figure 2). β-blockers were demonstrated to block calcium channels in the retina [82], and the neuroprotective effect of betaxolol and the nonselective β-blockers metipranolol and timolol, is thought to be elicited through reduction in sodium and calcium influx through voltagesensitive channels [83]. Levobetaxolol is a more effective neuroprotectant than timolol, likely owing to greater capacity to block sodium and calcium influx [61]. Additionally, levobetaxolol may blunt ischemic injury by upregulation of BDNF mRNA in the retina [84]. 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 [85]. Prosurvival pathways downstream of astrocyte activation may also play a role in β-receptor-mediated neuroprotection [86].

Aside from ion channel regulation, β-blockers have long been recognized to alter vascular dynamics, both systemically and in the eye. The β-adrenoreceptor receptors are localized to the ciliary epithelium and vascular smooth muscle, so β-blockers are intimately involved not only in the mediation of aqueous humor production, but also smooth muscle relaxation. While β-receptors have long been known to localize to both retinal arteries and veins [87], β-adrenergic binding sites also localize to vessel-free areas of the neural retina and optic nerve [77,88,89]. Blockers such as betaxolol have been demonstrated to increase blood velocity in the human ONH, thus supporting the hypothesis that mediation of vasculature effects may temper ischemia-induced RGC injury [90].

Of note, although β_2-agonists are not currently marketed as antiglaucoma medications, recent work has demonstrated potential neuroprotection via β_2-receptor activation and microglial inhibition, possibly by induction of β-arrestin 2 and modulation of glutamate homeostasis [91]. Additionally, β_2-adrenoceptor agonists promote anti-inflammatory and neurotrophic actions in nonglaucoma animal models of excitotoxicity [92].

Prostaglandin analogs

Prostaglandin analogs reduce intraocular pressure by enhancing uveoscleral outflow and are welltolerated with few systemic side effects. Additionally, they are considered advantageous from a compliance standpoint owing to their potency; the drugs are also useful in experimental models [93]. Pharmacological evidence suggests that bimatoprost acts by binding 'prostamide' receptors at the trabecular meshwork [94], the site of uveoscleral outflow. A secondary neuroprotective effect has also been recognized in prostaglandin analogs used to topically treat glaucoma. For example, topically applied latanoprost reduced the number of apoptotic RGCs following optic nerve crush [95], while the drug also exerts a neuroprotective effect on cells challenged by glutamate toxicity [96,97].

Multiple pathways for the anti-apoptotic effect of prostaglandin analogs have been proposed (Figure 3). It has been suggested that latanoprost may work by negative feedback on neuronal COX-2 activity, as it prevented lactate accumulation in the retinal tissue of animals subjected to acute ischemia [96]. Additionally, this same study found that COX-2 activity was reduced by both arachidonic acid and latanoprost in RGCs exposed to excess glutamate and that inhibition of inducible nitric oxide synthase occurred with the same drug concentrations. Latanoprost may also exhibit a direct anti-apoptotic effect via neurite outgrowth and caspase-3 inhibition, mediated by p44/p42 mitogen-activated protein kinase [98,99]. There are several other hypotheses regarding secondary neuroprotective mechanisms for prostaglandin analogs, including effects on ocular and ONH hemodynamics [100,101].

Carbonic anhydrase inhibitors

Carbonic anhydrase (CA) inhibitors are established as hypotensive agents, diuretics and antiepileptics, with additional use in the management of gastric and duodenal ulcers, neurological disorders and osteoporosis. CA-II is the isoenzyme that plays a role in aqueous humor production in the human anterior segment [102]. Dorazolamide and brinzolamide both potently inhibit CA-II and significantly decrease aqueous levels [102]. By acting upon CA-II, acetazolamide's inhibition of sodium accession decreases bicarbonate formation in the ciliary epithelium [103]. While CA activity localizes histochemically in the retina to Müller cells, cones and the pigment epithelium [104], distribution of the CA inhibitor trifluormethazolamide in tissue showed high concentrations in the ciliary body [105]. In retinal tissue in culture, the CA inhibitor dorzolamide reduced apoptotic pathways with exposure to methylglyoxal and glyoxal (intermediates of advanced glycation end products) and H_2O_2 [106].

This class of medications also demonstrates a vasodilatory effect [107], likely through a mechanism similar to CO_2-induced changes [108–110]. CA inhibitors increase cerebral blood flow following systemic administration [107,111], and ocular blood supply increases topical application [112]. Furthermore, membrane-associated CA activity within neuronal processes is also likely to modulate the pH of extracellular fluid, which can affect metabolic activity [106,113]. Additionally, ocular pulse amplitude increases following dorzolamide administration [114,115]. However, no changes were noted in ONH blood flow following dorzolamide administration in healthy human subjects [116].

A word on NMDA receptor antagonists

NMDA receptor antagonists (memantine in particular) have received wide attention as potential neuroprotective agents through their suppression of potentially excitotoxic pathways [117–119]. The putative neuroprotective action of NMDA receptor antagonists occurs through the reduction of potentially excitotoxic signaling due to excess glutamate [120], which is the primary mediator of excitatory neurotransmission in the mammalian CNS. It binds to three classes of ionotropic receptors, as well as metabotropic subunits, although its toxic effects are primarily mediated by binding of NMDA receptor subunits [121]. An excess of glutamate causes subsequent release of excess intracellular calcium (Figure 4), leading to neuronal death [121–123]. Excitotoxicity through excessive glutamate and stimulation of glutamate receptors (such as the NMDA receptor) has been implicated at various stages of neurodegenerative diseases [123]. NMDA receptor antagonists therefore probably exert their neuroprotective effects by directly inhibiting already metabolically stressed neuronal cell types from responding to excess glutamate.

Expert commentary

The concept of employing neuroprotectant medications to slow or even prevent irreversible glaucomatous damage to the optic projection is undoubtedly appealing. An extreme viewpoint might foresee the day when chronic IOP management is no longer relevant. The literature we have reviewed indicates that most of the common drugs used as part of a topical hypotensive regimen have direct neuroprotective properties independent of their action in the anterior chamber. These mechanisms include neuronal, glial and vascular pathways. However, most of the work described has been completed in animal models, and it is difficult to extrapolate both the mechanisms and the potential for direct neuroprotection of such medications to human patients. Careful clinical trials are necessary, as in the Low-Pressure Glaucoma Treatment Study, which recently demonstrated a protective effect of topical brimonidine in the absence of overtly elevated IOP [124]. This is especially important, since we often presume that secondary neuroprotective use needs to be optimized

for direct retinal and/or optic nerve delivery. In the burgeoning age of personalized medicine, we must also emphasize the importance of interplay between genetic and environmental factors in influencing not only the onset and progression of glaucoma, but also the response to treatments.

Obviously, potential side effects of such potent drugs must be fully understood and adequately controlled prior to systemic or targeted delivery in human patients. Most of the medications with secondary neuroprotective effects we have described act upon receptors that are generally distributed across multiple organ systems. The prevention of undesired side effects is no small feat and one that must be taken seriously in at-risk populations with multiple comorbidities.

Finally, the methods by which one may directly deliver neuroprotective medications to the retina and optic nerve represent a growing industry and a matter of considerable debate. The attraction for direct delivery is to avoid the primary difficulty that physicians encounter with topical medications, which is patient compliance. Topical use of neuroprotective medications would require efficient diffusion through the aqueous humor to the posterior segment and adequate permeability through the inner limiting membrane to reach a sufficient concentration for therapeutic efficacy. Intravitreal injections are a solution to patient compliance and delivery to the posterior segment, but raise the risk of infection and patient discomfort, assuming that adequate penetration and dosing is possible.

Five-year view

Currently, IOP is the only modifiable risk factor for glaucoma and the primary target of most glaucoma therapeutics. Several currently marketed medications may confer secondary neuroprotective benefits to the retina and optic nerve. In particular, a substantial body of empirical evidence suggests the α_2-adrenergic agonists (e.g., brimonidine) hold particular promise in abating the earliest pathogenic events in glaucomatous RGC degeneration [69,70]. As the neuroprotective mechanisms of disparate drug classes appear to work via different pathways, combination therapies may be the ideal method of combating neurodegeneration in glaucoma for those who do not respond to hypotensive regimens. In fact, synergistic neuroprotective effects using β_2-agonists and NMDA-receptor antagonists have already been demonstrated following stroke [125]. Over the coming years, current glaucoma medications marketed in combination formulations may help overcome progression to vision loss for nonresponders. The fundamental problem for neuroprotection does not seem to be a lack of available drugs, since the major hypotensives discussed here also demonstrate at least some neuroprotective effect in experimental systems. The problem is getting the drug to where it is needed in sufficient concentration to exert a sustained effect.

As the neuroprotective signaling pathways effected by common hypotensive drugs used in glaucoma are elucidated in greater detail, future neuroprotective treatments will likely target intermediates to abrogate degenerative pathways as a way to avoid systemic or other unwanted side effects. The overlap between glaucomatous neurodegeneration and other degenerative diseases of the CNS, such as Alzheimer's or amyotrophic lateral sclerosis, encourages cross-fertilization between fields. Mechanisms involving glial signaling or neurovascular interactions are of increasing relevance, not only in chronic disease, but also in trauma (e.g., stroke). These too will represent additional therapeutic targets for glaucoma in the coming years. Although barriers to the approval of use of experimental therapeutic compounds are daunting, the significant morbidity of glaucomatous disease warrants continued investigation into the mechanisms and delivery of neuroprotective agents, especially those already approved to lower IOP.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Assess the relationship between IOP and the progression of POAG

- Distinguish topical treatments for POAG with neuroprotective properties

- Analyze the mechanism of neuroprotection of different topical therapies for POAG

- Evaluate the clinical use of topical therapies for neuroprotection

Box 1. Currently marketed topical hypotensive medications with putative neuroprotective properties

α$_2$-agonists

- Apraclonidine
- Brimonidine

β-antagonists

- Betaxolol
- Levobetaxolol
- Timolol

Prostaglandin analogs

- Bimatoprost
- Latanoprost
- Tafluprost
- Travoprost

Carbonic anhydrase inhibitors

- Acetazolamide
- Brinzolamide
- Dorazolamide

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Box 2. Targets of neuroprotective agents
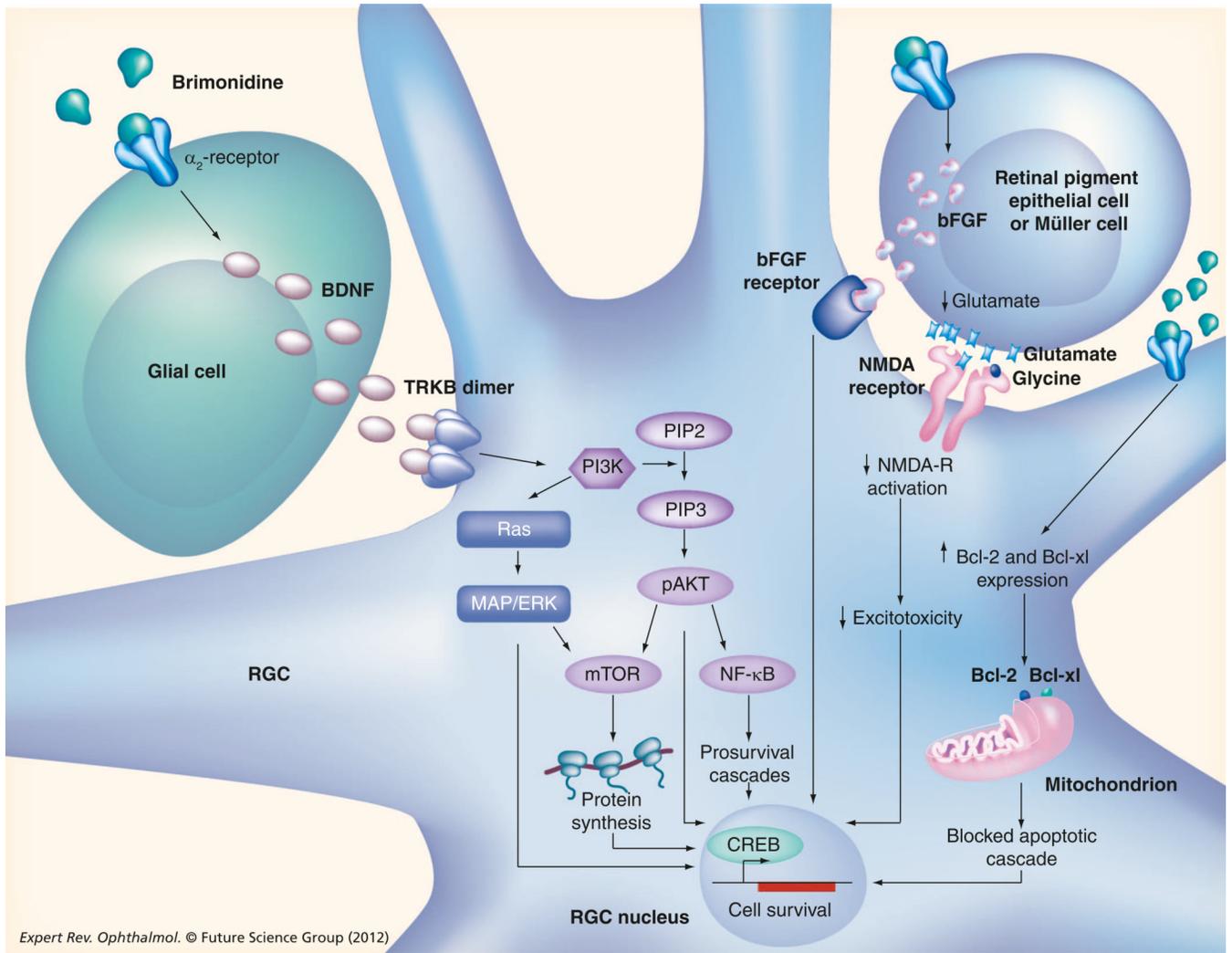
Direct neuroprotectants

- Cationic excitotoxicity

- Oxidative stress

- Mitochondrial by-products

- Calcium-induced injury

Indirect neuroprotectants

- Reduction of intraocular pressure

- Stimulation of glial cells

- Regulation of inflammatory mediators

- Augmentation of ocular blood flow

Key issues

- Intraocular pressure (IOP) is the only modifiable risk factor for glaucoma, although many patients have IOP within the normal range.

- The four most common classes of drugs used topically to lower IOP are α_2-agonists, β-antagonists/blockers, prostaglandin analogs and carbonic anhydrase inhibitors. Each of these classes has at least some experimental evidence of direct, secondary neuroprotective action on the retina and/or optic nerve.

- The α_2-agonists could exert a neuroprotective effect by upregulating expression of BDNF, basic FGF, the anti-apoptotic factors Bcl-2 and Bcl-xl, and the extracellular signal-regulated kinases and PI3K/Akt pathways.

- The β-antagonists could decrease glutamate-mediated NMDA receptor activation. Levobetaxolol also upregulates BDNF, while betaxolol increases tissue blood velocity in the optic nerve head, thus tempering ischemia-induced neuronal stress.

- Prostaglandin F_2 analogs are likely to exhibit a negative feedback mechanism on COX-2 activity and increase blood flow to the retina and optic nerve.

- Carbonic anhydrase inhibitors may increase retinal blood flow velocity and oxygenation, while additionally reducing the detrimental effects of advanced glycation end products and possibly oxidative stress. They can also exert an effect on extracellular pH by modulating membrane-bound carbonic anhydrase.

- Since the neuroprotective mechanisms of disparate drug classes appear to work via different pathways, combination therapies may be the ideal method of combating glaucomatous neurodegeneration.

- A key problem remains targeted delivery of known neuroprotectants in sufficient concentrations to exert a sustained effect.

- The overlap between other CNS neurodegenerative diseases encourages careful attention to mechanistic and therapeutic research being conducted in such disease fields.
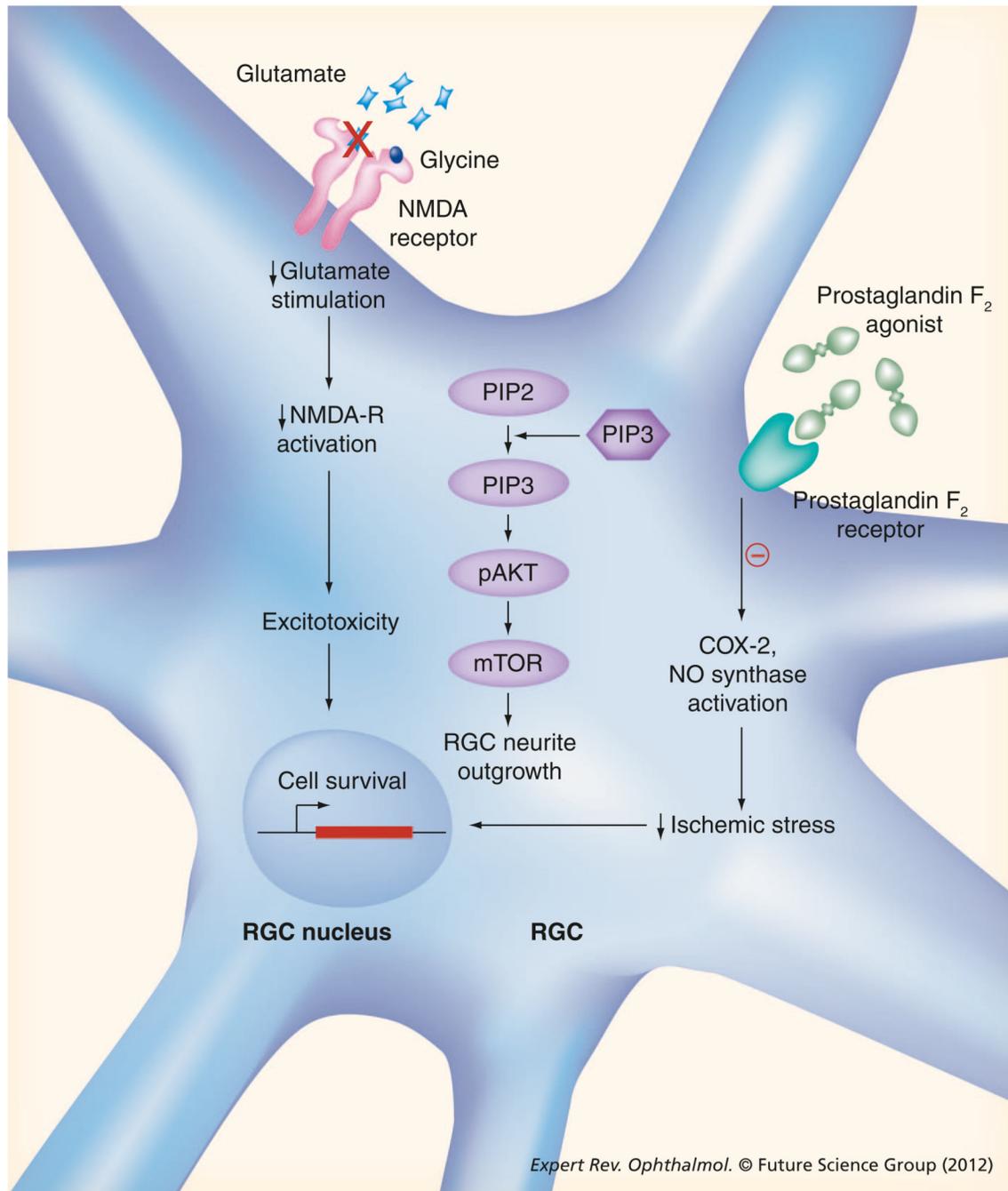
Figure 1. Possible mechanisms of neuroprotection mediated by α_2-adrenergic agonists
α_2-agonists such as brimonidine initiate multiple possible protective cascades. Direct binding of the α_2-receptor on RGCs could promote Bcl-mediated anti-apoptotic cascades, while binding to receptors expressed by glial or pigment epithelial cells could induce trophic signaling involving BDNF and bFGF, and their respective receptors.
bFGF: Basic FGF; NMDA-R: NMDA receptor; RGC: Retinal ganglion cell.
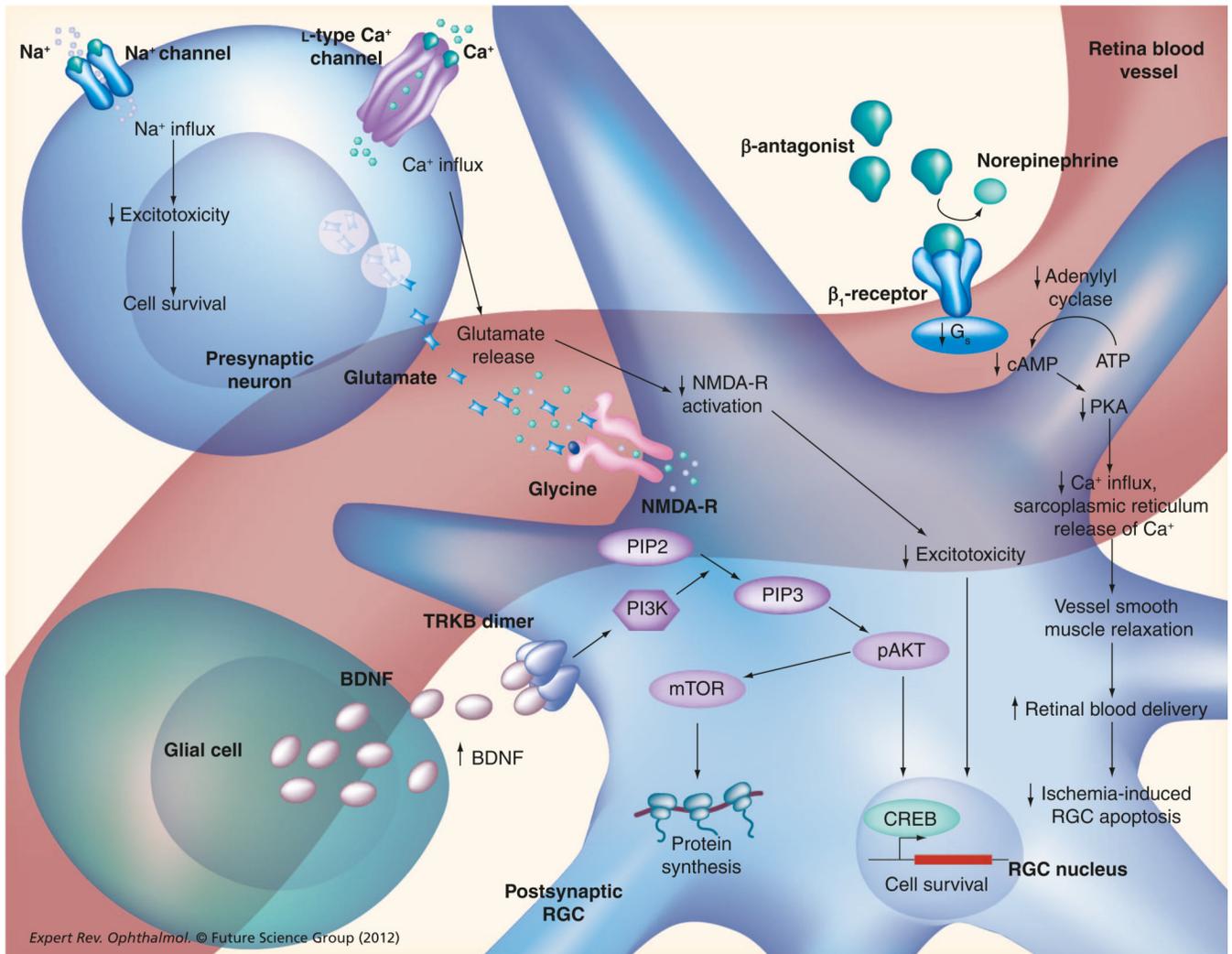
Figure 2. Putative neuroprotective actions of β-receptor antagonists

Based on known expression patterns, β-receptor antagonists could bind channels in presynaptic circuits to reduce the release of glutamate and postsynaptic activation of NMDA receptors on RGCs. Antagonists could also exert influence on receptors expressed by vascular elements, leading to increased blood supply and reduced ischemia-related stress. Finally, certain β-receptor antagonists upregulate expression of BDNF in retinal glia. NMDA-R: NMDA receptor; RGC: Retinal ganglion cell; TRKB: Tyrosine receptor kinase B.

Figure 3. Possible neuroprotective mechanisms of prostaglandin F$_2$ receptor agonists on retinal ganglion cells
Evidence suggests a role for prostaglandin agonists in reducing excitotoxic stress. Direct binding of prostaglandin receptors on RGCs could reduce COX-2-mediated induction of nitric oxide synthase.
NMDA-R: NMDA receptor; RGC: Retinal ganglion cell.
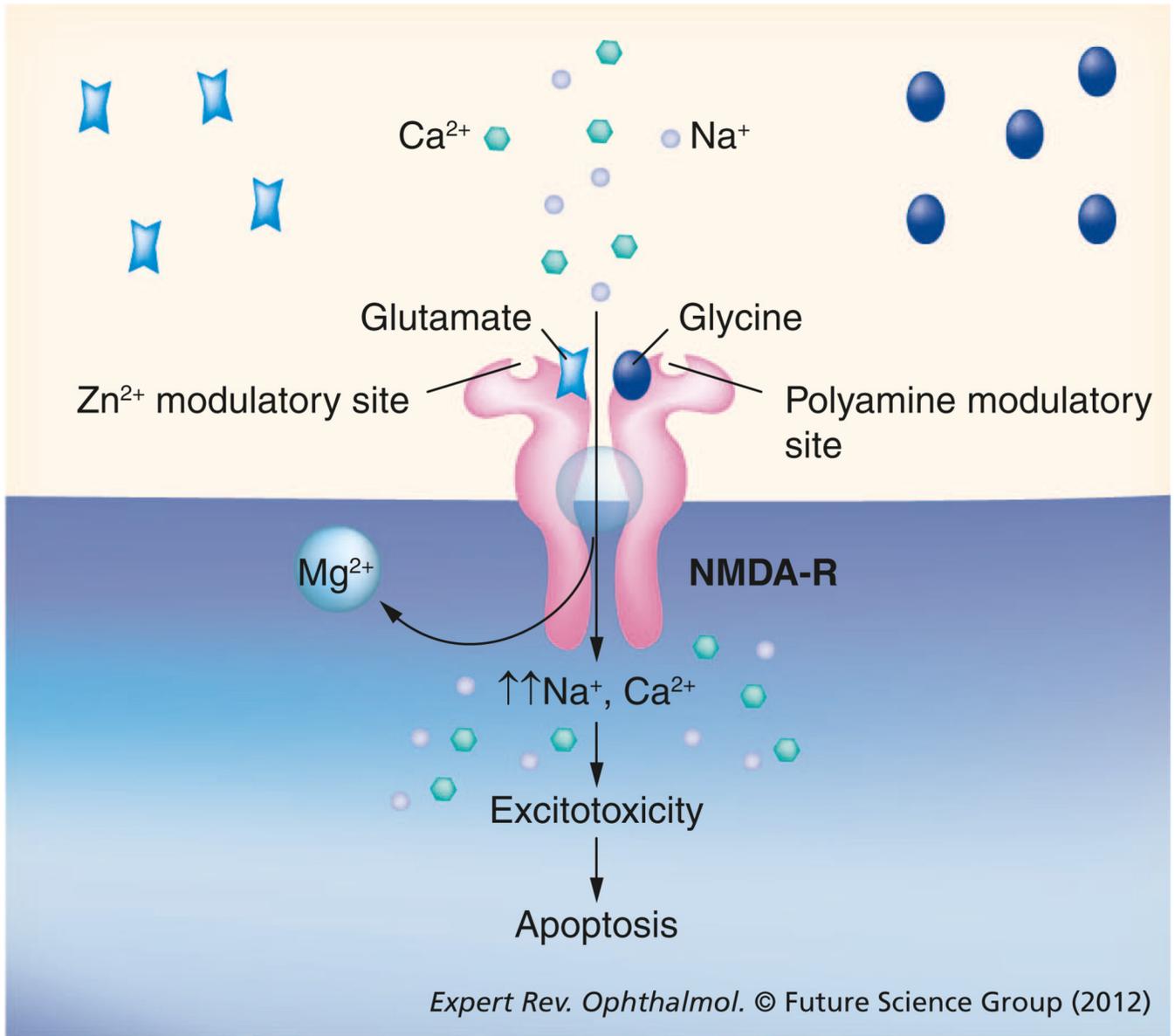
Figure 4. Interaction of glutamate with NMDA receptors
In many neurodegenerative conditions, excessive glutamate release from presynaptic
terminals binds to postsynaptic NMDA-Rs, depolarizing the postsynaptic membrane through
removal of the Mg^{2+} block. Subsequent influx and build-up of excess calcium leads to
excitotoxicity and neuronal apoptosis.
NMDA-R: NMDA receptor.