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Review Article

Glaucoma: role of neuroprotective agents

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ABSTRACT

Glaucoma is an optic neuropathy, considered as the second leading cause of blindness worldwide. Glaucoma is characterized by selective death of retinal ganglion cells (RGC) and a progressive loss of vision. Elevated intraocular pressure (IOP) is one of the most important risk factors for developing glaucoma and hence we mainly focus on lowering IOP to arrest the progression of glaucoma. However, many patients continue to demonstrate a clinically downhill course despite the control of initially raised IOP. In fact, some patients develop what is called normal tension glaucoma, not associated to an increased IOP. This emphasizes that several pressure-independent mechanisms are responsible for the development and progression of glaucomatous neuropathy and that high IOP and vascular insufficiency in the optic nerve head are only risk factors for the development of glaucoma, and are not the only target for the treatment of glaucoma. The reason is that the process of RGC death is thought to be biphasic, and the primary injury is followed by a slower secondary degeneration related to a noxious environment surrounding the apoptotic cells. This environment is characterized by changes in the extra-cellular ionic concentrations, increased amounts of free radicals, neurotrophins (NT) depletion and increased glutamate-induced excitotoxicity due to high extra-cellular glutamate levels, which binds to N-methyl-D-aspartate (NMDA) receptors leading to an abnormally high intracellular Ca2+ concentration. Neuroprotection is a process that attempts to preserve the remaining cells that are still vulnerable to damage, and the main aim of neuroprotective therapy is to employ pharmacologic or other means to attenuate the hostility of the environment surrounding the degenerating cells, or to supply the cells with the tools to deal with this aggression, providing resilience to the insult. Several agents have been reported neuroprotective in glaucoma, both in clinical assays, such as Ca2+ channel blockers, and in experimental studies, such as betaxolol, brimonidine, NMDA antagonists, nitric oxide synthase inhibitors, NT and *Ginkgo biloba* extract. Most neuroprotective agents for glaucoma have proved beneficial effects over RGC, not showing effects over IOP. However, when analyzing classically used medications for glaucoma, it becomes difficult to understand if its effect over the progression of glaucoma is due to neuroprotective pathways or by means of lowering IOP. The ideal anti-glaucoma drug would be one that when applied topically, reduces IOP, but also probes to reach the retina in appropriate amounts, and activates specific receptors in the retina to attenuate RGC death. In this review, we will examine currently advocated neuroprotective drug-based strategies in the potential management of glaucoma.

Keywords: Apoptosis, Cytoprotection, Gene therapy, Neuroprotective agents, Therapeutic use, Retinal ganglion cells

INTRODUCTION

Glaucoma is an optic neuropathy, specifically a neurodegenerative disease characterized by loss of retinal ganglion cells (RGCs) and their axons. In the past, glaucoma was viewed as a disease of raised intraocular pressure (IOP); however, it has become increasingly clear that elevated IOP is only one of the risk factors for this disease. Recent evidence indicates that lowering IOP does not prevent the progression in all patients and that progression can continue despite effective lowering of IOP. This was clearly depicted in the advanced glaucoma intervention study (AGIS) trial,[1,2] collaborative normal tension glaucoma study,[3,4] the collaborative initial glaucoma treatment study trial,[5] and the early manifest glaucoma trial.[6] As RGCs cannot

divide and regenerate, optic nerve damage is irreversible. It is, therefore, imperative that these cells are kept alive. The term neuroprotection refers to mechanisms within the nervous system, which protect neurons from apoptosis or degeneration, for example, following a brain injury or as a result of chronic neurodegenerative diseases. It has been a common approach that has been used to treat a variety of chronic neurodegenerative diseases such as Parkinson's and Alzheimer's disease, to name a few. Numerous theories of neuroprotection in glaucoma have been drawn from these neurodegenerative conditions, where the loss of the cells is targeted instead of the disease process by which these losses occur. This approach attempts to accelerate or impede specific biochemical pathways that may prevent neuronal injury or accelerate neuronal recovery. Hence, any therapy that prevents, retards or reverses apoptosis-associated neuronal cell death resulting from primary neuronal lesions is neuroprotective.

Therefore, neuroprotection in glaucoma is aimed at protecting those neurons that are damaged or likely to be damaged in glaucomatous optic neuropathy, which consists of neurons along the entire visual pathway, chiefly the RGC axons. This strategy is an addition to that achieved by IOP lowering alone. Even though any treatment approach that preserves RGCs in glaucoma could be described as neuroprotective, the term has been limited by many researchers to describe a drug that directly interacts with neuronal or glial elements within the optic nerve head.

Consequently, the endpoint of neuroprotection in glaucoma offers a means to prevent the irreversible loss of those cells in glaucoma, especially where the particular etiology is either idiopathic or differs from patients to patients.

In recent years, the focus of glaucoma research has shifted toward neuroprotection as the traditional strategies of lowering IOP have been shown to be unable to prevent progressive vision loss in some glaucoma patients. As a result various neuroprotective drug-based approaches have been shown capable of reducing the death of RGCs, which is the hallmark of glaucomatous optic neuropathy.

PATHOGENESIS OF GLAUCOMATOUS DAMAGE AND IMPORTANCE OF NEUROPROTECTION

Actual events leading to the death of RGCs has delineated several mechanisms that may be responsible for RGC death:

1. Neurotrophin (NT) withdrawal due to retrograde axoplasmic transport block
2. Glutamate induced excitotoxicity
3. Free radical generation
4. Nitric oxide neurotoxicity
5. Apoptosis.

NT withdrawal

Mammalian neuronal growth and maintenance depend upon the viability of retrograde axoplasmic transport of soluble growth factors called NT.[7] The NT supplied to the RGCs are small peptides that function to regulate cellular metabolism by attaching themselves to neuronal target-cell receptors. As the nervous system develops, the surplus of neurons produced is subsequently eradicated by apoptosis. Neurons require neurotrophic growth factors, which are acquired by retrograde axoplasmic transport. These growth factors, known as NT, regulate cellular metabolism hence maintaining the normal cellular milieu.[7] Thus, where neurotrophic support is absent due to retrograde axonal transport block, RGCs die. This group of small growth peptides comprises brain-derived neurotrophic factors (BDNF), nerve growth factors (NGF), NT-3 and NT-4.[8,9] Lack of BDNF and NGF secreted by RGC targets results in apoptosis of developing RGC though it is postulated that it has almost no effect on the survival of mature RGCs since retrograde transport of NT factors persists along adult RGC axons. Hence, in glaucoma, blockade of axonal transport results in NT deprivation leading to neuronal cell death.[9-16]

Apoptosis

Apoptosis refers to a common mode of cell death. It is a subtle process where the cell initiates a death program and commits suicide resulting in cell shrinkage, genomic fragmentation and nuclear pyknosis.[11] This sequential occurrence of cell death processes appears to be biphasic, and research in optic nerve injury models has shown both fast and slow phases of RGC degeneration.[12]

There are many triggering factors for apoptosis, be it extracellular or intracellular events. These include trophic factor deprivation or oxidative damage, both of which have been postulated to induce RGC apoptosis in glaucoma. A principle class of intracellular apoptotic regulators is the B-cell lymphoma 2 (Bcl-2) family of mitochondrial membrane-bound proteins. Athough some proteins in this family inhibit apoptosis (e.g., Bcl-2, Bcl-X_L), others promote it (e.g., Bax, Bad, Bid).

Caspases are proteases that execute the dismantling and demolition of apoptotic cells. Caspases are categorized into two broad groups: initiators (e.g., caspases 8 and 9) which activate other caspases and effectors (caspase 3) which cleave specific substrates involved in the cellular disassembly. Some experimental glaucoma models have shown that the initiator caspases are activated, while inhibition of the effector caspases can be neuroprotective.[13-22] Calcium overload is also responsible for activation of calpane and caspase cascades, leading to apoptosis.[15]

Glutamate induced excitotoxicity

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS) and is present in neurons in very high concentrations. Glutamate induced excitotoxicity occurs when extra-cellular glutamate levels are increased, either due to increased release or decreased uptake from the synapse. High glutamate concentrations activate several types of cell receptors, including N-methyl-D-aspartate (NMDA) receptors that can allow entry of excessive amounts of calcium. Abnormally high Ca2+ concentration leads to inappropriate activation of complex cascades of nucleases, proteases and lipases. They directly attack cell constituents and lead to the generation of highly reactive free radicals and activation of the nitric oxide pathway.[16] The resulting interaction between intermediate compounds and free radicals leads to DNA nitrosylation, fragmentation and activation of the apoptotic program.

Free radical generation and oxidative stress

Free radicals are a byproduct of oxidative metabolism. The high metabolic activity of retinal tissues render RGCs, especially vulnerable to oxidative stress.[17] Free radicals interfere with macromolecular cellular constituents of the cells and further lead to derangement of protein breakdown, lipid peroxidation and nucleic acid degeneration, resulting in cell death.[18] To counteract this, ocular tissues have highly efficient antioxidant mechanisms that include the superoxide dismutase-catalase system, ascorbic acid, and reduced glutathione.

Nitric oxide neurotoxicity

Nitric oxide neurotoxicity occurs through the reaction of nitric oxide with superoxide anion to form peroxynitrite and other more reactive free radical species. Peroxynitrite acts by s-nitrosylating both proteins and nucleic acids, thus destroying them.[19]

Rationale for neuroprotection

The path to clinical use of neuroprotectant has been long and uneven. Although the possibility of non-IOP-lowering therapy for glaucoma was first recognized in 1972 by Becker et al. with the use of diphenylhydantoin for treatment of visual field loss in primary open-angle glaucoma, only of late significant advances have been made in the understanding of the mechanisms for death of retinal neurons.[20]

The randomized clinical glaucoma trials have demonstrated progression of the disease despite significant pressure lowering. A retrospective subanalysis of the AGIS data showed that the variation of IOP readings across office visits was more important than the absolute level.[21] Asrani et al. suggested that the diurnal IOP range and range over multiple days were significant risk factors for progression, even after taking into account office IOP, age, race, gender, and visual field damage at baseline.[22] Thus, glaucoma will progress even in patients with effective IOP lowering, rendering it a good candidate for neuroprotection.

NMDA receptor antagonists

Excess glutamate leads to NMDA receptor overactivation as well as excitotoxicity. Hence, using NMDA antagonist would be an efficient way to prevent RGC loss where excitotoxicity is implicated.[23] The earliest experiments used MK-801 which completely blocks normal glutamatergic neurotransmission, which is required for normal CNS function, and is, therefore, inappropriate for clinical use.[24] Experimental models of retinal ischemia induced by transient elevation of IOP have shown that NMDA inhibition with MK-801 confers neuroprotection by decreasing the expression of bad and transient deactivation of the pro-survival kinase Akt pathway.[25] Memantine, being well tolerated, has been approved for its use in Alzheimer's disease and vascular dementia as it is a highly effective neuroprotective agent as demonstrated in acute animal models of RGC death. The largest randomized, progressive, Phase 3 clinical trial on neuroprotection studying the safety and efficacy of memantine for open-angle glaucoma has been completed, but it disappointingly failed to meet its primary endpoint.

Neurotrophic factors

Various studies in experimental models have shown that neurotrophic factors, especially BDNF and ciliary neurotrophic factor, can enhance survival of RGCs after optic nerve injuries, but there are to date no adequately powered clinical trials to substantiate this in humans.[26] Recent studies have shown that a combination of BDNF and LINGO-1 (a CNS-specific leucine-rich repeat protein) antagonist enhances long-term RGC viability. Most of the investigations have been focused on BDNF.

Anti-apoptotic agents

Several pathogenic mechanisms have been proposed to induce apoptotic RGC death in glaucoma. These include reduced neurotrophic factors and cytokine deprivation to neurons, altered intracellular calcium levels, reactive oxygen species and excitotoxicity due to raised extracellular levels of certain neurotransmitters and neuromodulators.[26] Enhancing mitochondrial function may also inhibit apoptosis. Recent studies have shown that supplements of creatine, α-lipoic acid, nicotinamide and epigallocatechin-gallate, which act by counteracting oxidative stress, promote mitochondrial function and confer neuroprotection.[25]

The use of brimonidine activates anti-apoptotic extracellular signal regulated kinase and Akt, which in turn enhance the production of Bcl-2 and Bcl-X_L.[16] The second approach is to block the apoptotic machinery using caspase inhibitors.[17-21]

Caspases are the effector enzymes that disassemble cellular contents during apoptosis. Calpeptin, a calpain-specific inhibitor has been shown in glaucoma experimental models to confer neuroprotection.[14]

Nitric oxide synthase (NOS) antagonists

Inhibition of NOS using 2-aminoguanidine, i-NOS and L-N [6-(1-iminoethyl) lysine 5-tetrazole amide has been shown to be neuroprotective in experimental glaucoma models.[12] Nipradilol, a β- and α_1 antagonist has also been shown to be neuroprotective.

Antioxidants

RGC death by NMDA-induced toxicity may be reduced by antioxidants and free radical scavengers such as vitamins C and E (α-tocopherol), superoxide dismutase and catalase. *Ginkgo biloba* (EGb761), apart from increasing blood flow, has been also found to have a free radical scavenger property.[19] Its extract is also known to preserve mitochondrial metabolism and enhance ATP production in various tissues.

Calcium channel blockers

Calcium channel blockers such as nifedipine and verapamil may exert neuroprotection by increasing blood flow to the RGCs.[10] In addition, they also improve glutamate metabolism and hence cause efficient homeostasis in the optic nerve head.[10] However, there are concerns that by also causing systemic hypotension these agents can worsen retinal ischemia due to a reduction in perfusion pressure.

Currently available topical medications

α_2-adrenoceptor agonist

α_2-Adrenoceptors are located in the ganglion cell layer of the retina.[19,20] Activation of these receptors inhibits neuronal cell death through a complex, but independent pathway. There is mounting evidence implicating that α_2-adrenoceptors inhibit the pro-apoptotic pathway, trophic factor release,[22] as well as glutamate release, providing neuroprotection. Brimonidine, being a highly selective α_2-adrenoceptor agonist, which lowers IOP essentially by decreasing aqueous humor inflow, has been established to be neuroprotective to RGCs in this manner. There is an ongoing large randomized controlled clinical trial of neuroprotection called the low-pressure glaucoma treatment study comparing brimonidine and timolol.

β-adrenoceptor antagonists

Another category of widely available drugs is the β-adrenoceptor antagonists, which is further subdivided into the β_1-selective (e.g., betaxolol) and non-selective (e.g., timolol) β-blockers. All β-blockers lower IOP via inhibition of β_2-adrenoceptors presents on the ciliary epithelium, thus reducing aqueous humor flow. The neuroprotective elements of β-blockers are believed to be mediated by inhibition of calcium and sodium ion influx into neurons, which occurs in hypoxia, ischemia and excitotoxicity.

Prostaglandins (PGs)

It is well-accepted that in the pathogenesis of ischemic and inflammatory injuries, PGs including $PGF_{2\alpha}$ are implicated. They are potent vasoconstrictors and can possibly play a role in the pathogenesis of ischemia and inflammation; however, there is currently no strong evidence to suggest that they are toxic to the retina or optic nerve. Drugs such as latanoprost, travoprost, bimatoprost and unoprostone enhance aqueous outflow, thus reducing IOP. Latanoprost exerts its neuroprotective effects by impeding glutamate and hypoxia-induced apoptosis and is postulated to act via negative feedback on cyclooxygenase-2 activity. There have been no large clinical trials focusing on the neuroprotective effects of PGs.[6-16]

Carbonic anhydrase inhibitors

Another major group of drugs is the carbonic anhydrase inhibitors, e.g. dorzolamide and brinzolamide, which are selective carbonic anhydrase isoenzyme II inhibitors located in the ciliary epithelium. Carbonic anhydrase isoenzyme II inhibition ensues a reduction in aqueous humor formation as well as increases blood supply to the choroid and optic nerve head, regardless of IOP, though the mechanism is unknown. Although it seemed to be neuroprotective in a rat hypertension model, the level of neuroprotection correlated with the level of IOP reduction, which might mean that the neuroprotection conferred by these agents may be due to the IOP reduction rather than its direct neuroprotective properties. Until date, there is inadequate evidence to show that this group of drugs is successful in providing neuroprotection.[22-24]

Other compounds and alternative therapies

Erythropoietin, being a hematopoietic cytokine, has shown to hold amazing neuroprotective properties in pre-clinical models.[27] Endocannabinoids play a big role in CNS neurodegenerative diseases. They have vasodilatation properties giving them neuroprotective effects. There are also many natural compounds such as omega-3 fatty acids, carnitine, coenzyme Q10, citicoline, curcumin, danshen (*Salvia miltiorrhiza*) and resveratrol that potentially confer neuroprotection via various mechanisms. However, there are no large clinical trials to date that support the use of these compounds in the treatment of glaucoma.[27]

Gene therapy

The current core of gene therapy is targeted against apoptotic factors. Candidate agents are deprenyl, a monoamine oxidase inhibitor (anti-parkinsonism drug), which increases the gene expression of factors that halt apoptosis, and flunarizine and aurintricarboxylic acid, which have shown promising results in retarding apoptosis following light-induced photoreceptor cell death.[28]

Intense research in gene therapy has made it an emerging therapeutic possibility in glaucoma management. Advances in the expression of apoptosis-involved genes or their protein products have demonstrated neuroprotective capacity *in vitro*. Several gene families have been identified that play either positive or negative roles in determining whether a cell will undergo apoptosis. Caspases are cysteine proteins that both propagate apoptotic signals as well as carry out disassembly of the cell. Many triggers activate caspases including increased intracellular calcium, free radicals and adenosine 3'5'- cyclic phosphate.[29] The prototype of the mammalian caspase is interleukin-1b converting enzyme. The main inhibitors of apoptosis are Bcl-2 and related proteins. They have multiple complex functions, such as inhibiting intermediate proteins that activate caspases.[30] One of the primary regulatory steps in apoptosis is the activation of the tumor suppression protein, p53. This protein functions as a transcription factor that can up-regulate the expression of the pro-apoptotic gene bax and down-regulate the expression of the anti-apoptotic gene Bcl-2. Other promising compounds include flunarizine and aurintricarboxylic acid, which apparently delay apoptosis after light-induced photoreceptor cell death.[30]

CONCLUSION

Glaucoma represents a complex multifactorial disease that produces an accelerated rate of ganglion cell atrophy related to a consortium of pathogenic mechanisms that not only most certainly involve IOP but also include defective autoregulation and ischemia, neurotrophic factor deficiency, glutamate-mediated excitotoxicity, immune-related phenomenon, weak collagenous support at the lamina cribrosa, intracellular calcium influx, and free radical damage. IOP lowering will continue to be the mainstay treatment for glaucoma. The question of alternative non-IOP-lowering therapies directed at preventing further progression has become of interest to both the desperate patient and the treating physician. Based on new, emerging research, neuroprotection has promise for preventing RGC death, independent of IOP. It is evident that pharmacological neuroprotection for glaucoma without a doubt represents an exciting development in the pursuit for a treatment modality for this debilitating disease.

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