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# BEYOND IOP: NEUROPROTECTION AS A THERAPEUTIC STRATEGY IN GLAUCOMA

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**Abstract**

*Glaucoma refers to a degenerative optic neuropathy and one of the main causes of global blindness. Intraocular pressure (IOP) continues to be the major stackable risk factor in glaucoma, and the majority of existing modalities of treatment of glaucoma strive to lower IOP in order to exclude the further damage. Nevertheless, a considerable percentage of patients develop retinal ganglion cell (RGC) loss, and decline of visual fields even after having attained target IOP values. This also highlights the dire need of adjunctive treatments that are not restricted to IOP management. Neuroprotection, which is the intervention to prevent and decrease hypothetically occurrence of neuronal injury and apoptosis, has become a potentially fruitful path of therapy of glaucoma. The current paper examines the scientific explanation to the application of neuroprotection in glaucoma general findings regarding the cellular processes that lead to glaucomatous damage, including oxidative stress, excitotoxicity, mitochondrial disorder, and neuroinflammation. The existing and developing neuroprotective treatments are presented; among them, it can be brimonidine and memantine, antioxidants, and mitochondrial stabilizers. Moreover, modern forms of treatment (gene therapy, interventions based on stem cell usage) are tested regarding their effectiveness in treating RGC survival and axonal regrowth. Although there has been much preclinical advancement, translation of these therapies into the clinical domain is rather difficult because there are no sensitive biomarkers and standard achievable outcome measures of neuroprotection. Our conclusion is that integration of neuroprotective approaches with the current established treatment models of glaucoma would substantially benefit population at large by preventing visual deficiency more efficiently. With improvements in research, neuroprotection is on the verge to become a part and parcel of holistic glaucoma management.*

*Keywords: neuroprotection, retinal ganglion cell, glaucoma, intraocular pressure, optic nerve, N-methyl-D-aspartate receptor, brimonidine, stem cell, biomarker.*

**Introduction**

Glaucoma is a progressive and chronic optic neuropathy, which is among the top causes of incurable blindness the world over (Quigley & Broman, 2006). Glaucoma is an ailment which is typified by the setback of retinal ganglion cells (RGCs) and axons and is usually doubtlessly progressing without notice until severe defect in the visual field has been developed. Although the increase of intraocular pressure (IOP) is known to be the main modifiable risk factor, most patients still lose vision even after reaching the target IOP rates (Weinreb et al., 2014). This finding emphasizes the fact that glaucomatous damage is highly multifactorial and frames the constraints of the pressure-lowering medication. An adjunctive treatment option that has come to the fore is neuroprotection which is the preservation of the neuronal structure and functioning without interventions of IOP (Levin, 2003). Neuroprotection is conceptualized by the increase in the bio-pathologic complexity of the retinopathies in glaucoma, such as excitotoxocity, oxidative stresses, mitochondrial aberrations, and inflammation (Nickells, 2007). The processes cause apoptosis of the RGCs, and they are not completely covered by the IOP-lowering treatments. Therefore, focusing on these pathways provides a new way of slowing or preventing a neurodegenerative process that characterizes glaucoma. A number of experimental neuroprotective agents have been found in preclinical models. As an example, brimonidine has provided neuroprotective effect through alpha-2 adrenergic routes (Yoles et al., 2003), whereas memantine, NMDA receptors antagonist, has shown promise in animal studies but had inconclusive effects in clinical studies (Danesh-Meyer, 2011). Moreover, the improvement of gene therapy and stem cell technologies also offer new potential of retina regeneration and neurorestoration (Almasieh et al., 2012).

In light of these, neuroprotection is a paradigm level treatment in the glaucoma treatment. The paper has discussed the mechanisms involved in the neurodegeneration of glaucoma, reviewed pharmacologic and biologic neuroprotective interventions and clinical challenges of the neuroprotective approaches and direction in applying these approaches in glaucoma management.

**Objectives**

1. To analyze the limitations of intraocular pressure (IOP)-lowering therapies in halting glaucoma progression.
2. To explore the molecular and cellular mechanisms responsible for retinal ganglion cell (RGC) degeneration in glaucoma.
3. To evaluate current and emerging pharmacological agents with neuroprotective potential in glaucoma management.
4. To investigate innovative therapeutic approaches, including gene therapy and stem cell-based strategies, aimed at promoting retinal regeneration.
5. To highlight the challenges in translating neuroprotective research into clinical practice, including the need for sensitive biomarkers and standardized endpoints.
6. To propose a comprehensive treatment framework that integrates neuroprotection with conventional IOP-lowering strategies for improved long-term patient outcomes.

**IOP-Lowering Therapies Limitations**

Lowering the intraocular pressure (IOP) continues to form the mainstay of the glaucoma treatment. Independently of whether they are attained using topical medications, laser trabeculoplasty, or surgical offerings, IOP-lowering measures seek to examine the mechanical and vascular pressure on the optic nerve head (Weinreb et al., 2014). Nonetheless, there exists a great deal of clinical evidence, demonstrating that very many glaucoma patients still develop disease progression even when their IOP has been brought down to and is held at target values. This has been especially witnessed in normal-tension glaucoma (NTG) which is a type of the disease where damage of the optic nerve occurs with a normal IOP still under the statistically normal range (Leung et al., 2010).

In a number of milestone studies, it has been demonstrated that IOP reduction can reduce rate of progression but it does not completely stop it in every patient, e.g., Collaborative Normal-Tension Glaucoma Study (CNTGS) (Anderson et al., 2003). Moreover, the results of Early Manifest Glaucoma Trial (EMGT) proved the fact that IOP reduction does have a positive effect on the onset of visual field loss, but individual differences in the vulnerability to the optic nerve damage indicate that there exist IOP independent pathogenetic processes (Heijl et al., 2008).Moreover, IOP has also been losing its status as an informative biomarker of the disease activity as well. During the measuring of IOP, there will always be a variance as a result of circadian variations and the limitations of the measuring process (Asrani et al., 2003). Besides, in some patients IOP elevation can be preceded by structural and functional damage, causing late diagnosis and poor outcomes of management.

The other limitation is that the conventional IOP- lowering therapies although success in lowering pressure, do not actively enhance the survival of neurons. They do not promote the repair or replacement of injured retinal ganglion cells (RGCs) as well as they do not have any direct effect on the neurodegenerative cascade that defines glaucomatous optic neuropathy. Therefore, the desire to settle at the level of purely pressure-based therapy instead of more holistic approaches that embrace neuroprotective therapy is steadily increasing. IOP reduction is not an effective intervention on its own when it comes to dealing with every glaucoma patient. These restrictions have necessitated the research of Twenty-five adjunctive therapies to enhance the health of the optic nerves by manipulating non-pressure related pathways that cause damage in glaucoma.

**Mechanisms of Glaucomatous Neurodegeneration**

The view of glaucoma as a neurodegenerative disease is becoming widely accepted nowadays and the death of retinal ganglion cells (RGC) appears to represent the ultimate common route that the disease follows on its way to a permanently lost vision. Despite the high level of intraocular pressure (IOP) being among the most important risk factors, the pathophysiology of glaucomatous optic neuropathy has a variety of IOP-independent mechanisms to be discussed. Such mechanisms are glutamate excitotoxicity, oxidative stress, mitochondrial, and immune-mediated inflammatory processes which

are the driving and spreading factors of neuronal apoptosis in the retina and the optic nerve (Nickells, 2007).

Excitotoxicity is defined as the resulting destruction of excessive stimulation of glutamate receptors, especially NMDA ( N-methyl-D-aspartate ) receptors on RGC. Over-activation results in uncontrolled calcium inflow which in turn causes intracellular signaling cascades which lead to the failure of mitochondria and cell death (Neufeld et al., 2002). Researchers have also found raised levels of glutamate within the vitreous of eyes with glaucoma further incriminating this mechanism in the process of glaucoma.

Another important cause is oxidative stress that is caused by the imbalance between the cell generation of reactive oxygen species (ROS) and the cell antioxidant defense activity. It seems that the cause of aging RGCs is the dysfunction of mitochondrion, and gives rise to elevated ROS, which promote the fate of lipid peroxidation, DNA damage and apoptosis (Tezel, 2006). This is aggravated by damaged axonal transports to deny the RGCs of crucial life signals by the brain. Inflammation is of major importance too. Proinflammatory cytokines released by activated micro glia and astrocytes are reported to cause neurological injury thereby leading to neuronal damage (TNF- alpha) (Yang et al., 2011). Although certain inflammatory processes might be protective in their initiation, continued activation results in a toxic microenvironment that prevents RGC survival.

Lastly, increased evidence is that glaucoma is molecularly similar to other central nervous system (CNS) neurodegenerative disorders, including Alzheimer and Parkinson. These are misproteins, mitochondrial breakdown and synaptic breakdown (Calkins, 2012). The analogy indicates that glaucoma may be benefited by the treatment methods serving other diseases of the CNS. Finally, the neurodegeneration process in glaucoma is an under-defined issue that requires a combination of local eye and systemic mechanisms. Knowledge of such pathways is crucial towards the realisation of effective neuroprotective interventions that require the addressing of the biology of the disease irrespective of control of IOP.

**New Neuroprotective Agents**

Neuroprotection has been taking the center stage in glaucoma studies in the recent years given the short offerings of intraocular pressure (IOP)-reducing treatment. There are also a few pharmacological agents that have been considered to have potentials to prevent or even slow retinal ganglion cell (RGC) death and the maintenance of visual functions. One of them, brimonidine, an alpha-2 adrenergic receptor agonist has demonstrated neuroprotecting properties that are not limited to an IOP-lowering effect. There are clinical studies that reveal that brimonidine is very effective in preventing glutamate excitotoxicity and enhancing retinal blood flow as well as up-regulated neurotrophic factors like brain-derived neurotrophic factor (BDNF) which promotes the survival of the RGC (Yoles et al., 2003).There is also clinical promise on brimonidine. In a randomized clinical trial that compared brimonidine and timolol in normal-tension glaucoma, there was a slower development of visual field in patients on

brimonidine even though the IOP was well controlled in both arms (Krupin et al., 2011). But, the dropout rate on ocular allergy restricted the use of results and made it more important to come up with more acceptable formulations.

Memantine is another broadly-researched neuroprotective agent, an NMDA receptor antagonist used to treat Alzheimer disease. Memantine is supposed to prevent glutamate-mediated excitotoxicity, which is among the most important mechanisms of the damage to RGC. In early animal models, it was shown to be neuroprotective effectively; however, a phase III trial, an Allergan-sponsored trial, involving large numbers of multicentric human clinical trials was not able to show statistically significant visual field preservation in comparison to placebo (Danesh-Meyer, 2011). Although of clinical use, that use is not encouraging, memantine still appears as prototype of glutamate antagonists, and there may be more encouraging success with a modification of dosage or selection of patient. Additional antioxidant, mitochondrial, or neurovascular actions were demonstrated in citicoline, coenzyme Q10 and ginkgo biloba extract among other compounds (Parisi et al., 2015). These agents have elicited mixed success rates on small scale clinical testing trials but validation on bigger trials is necessary. In general, the fight against glaucoma with the help of neuroprotective agents is hopeful but complicated. Inconsistency in designing trials, rates of disease progression and the outcome measurement procedures makes it cumbersome to accurately measure the efficacy. However, continuous efforts in this field have the potential of changing the way glaucoma is handled by supplementing the conventional theories of restoring IOP.

**Innovative methods of Regeneration and Treatment**

Although research on pharmacological neuroprotection has comprised much research in glaucoma, it is hoped that emerging strategies of regenerative therapies will be able to create new avenues to restore visual functions in the long run. Stem cell-based interventions can be defined as one of the trends of this innovative shift since they can serve as not only neuroprotective but cell regenerative strategies. Gene therapy would seek to either modify gene expression in retinal ganglion cells (RGCs) or peripheral tissues so as to enhance cell survival. Delivery of neurotrophic factors including brain derived neurotrophic factor (BDNF) or ciliary neurotrophic factor (CNTF) is one of the most promising targets. These proteins promote neuronal growth and survival and their action is limited by their short half-life and adversely by their inability to permeate tissue. Introductions of these factors using viral vectors, most successfully utilizing adeno-associated viruses (AAVs), has resulted in prolonged expression in animal models causing a delay in RGC loss in experimental glaucoma (Martin et al., 2003). Despite good safety properties of AAVs, human trial is at a very early phase and has several challenges, such as targeting efficiency and immunity.

The other promising field is stem cell applications. It has been shown that transfection of eye with mesenchymal stem cells (MSCs) or induced pluripotent stem cell (iPSCs) provides neuroprotection to RGCs by secreting neuroprotective cytokines or even by possibly replacing them with themselves at

some points. The preclinical researches have demonstrated that MSCs produce growth factors that limit inflammation and oxidative stress, which provides a favorable microenvironment to native RGCs (Mead & Tomarev, 2016). Nevertheless, a replacement of RGCs by direct transplantation is still a far-fetched objective as a very complicated wiring of the axons is needed to reach central visual centers.

There is also research into the viability of optogenetics- the restoration of light sensitivity within surviving retinal neurons- and CRISPR/Cas9 gene editing as a means of repairing mutations involved with hereditary glaucoma. Although at this stage all these technologies remain experimental, we can still recognize the changing vision of glaucoma treatment, namely neuroprotection to a true neuroregeneration. Gene and stem cell treatment is the new age glaucoma therapy. Though numerous scientific and regulatory challenges still lie ahead, these solutions can transform the way in which glaucoma is treated, particularly in more severe cases where there is a substantial loss of RGCs.

**Conclusion**

Glaucoma is no longer considered as a disease of high intraocular pressure (IOP), but it has become a multifactorial disease of complex neurodegenerative process. In spite of the fact that IOP-lowering is the foundation of the clinical management, there is emerging evidence, which indicates that in many patients, progression still occurs even with the ideal pressure control. This is because of the acute future plans on adjunctive approaches that impact on the etiological processes of retinal ganglion cell (RGC) death, including excitotoxicity, oxidative stress, inflammation, and mitochondrial dysfunction. The neuroprotection, the aim of which is to maintain the RGC structure and functions independently of the IOP, has become an important and promising direction of treatment. The pharmacological strategies such as brimonidine and memantine have given promising responses in preclinical experiments, but clinical accomplishments have been elusive. The nonuniformity of the disease, absence of sensitive biomarkers to quantify the disease, and protracted times along which progression has to be assessed make it difficult to know the neuroprotective efficacy of the disease in human trials. However, these barriers are gradually being reduced by improvement in trial design and imaging technology.

As a parallel, alternatives to these interventions like gene therapy and stem cell-based treatment methods are catching up. Speaking about strategies, they provide neuroprotection, but also possible regeneration, particularly in severe cases, when depletion of neurons has already occurred. They are the future of individualized, regenerative glaucoma treatment even though they are currently in an experimental phase. It can be mentioned that focus on managing neuroprotective and regenerative approaches on top of IOP clinical management would help to preserve vision better and achieve better long-term outcomes. Further interdisciplinary research alongside creation of strong clinical endpoints and biomarkers will play a key role in transitioning these therapies out of the lab environment and into clinical practice. The implementation of neuroprotection into the daily practice can eventually transform the standard of glaucoma treatment in the 21st century.

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