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New Trends in Neuro-protection in Glaucoma

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Abstract

Recent advancements in neuroprotection for glaucoma have seen a shift towards multifaceted approaches targeting various aspects of the disease's pathophysiology. Traditional strategies were primarily focused on lowering intraocular pressure (IOP) but emerging trends highlight the importance of preserving retinal ganglion cells (RGCs) and their axons. Novel therapeutics aim to enhance neurotrophic support, reduce excitotoxicity, and mitigate oxidative stress, complementing IOP-lowering therapies for comprehensive management. Stem cell therapies, neurotrophic factors, and gene therapies show promise in promoting RGC survival and axonal regeneration. Additionally, the repurposing of existing drugs, such as calcium channel blockers and anti-inflammatory agents, for neuro-protection in glaucoma underscores the importance of exploring diverse mechanisms. These innovative approaches represent a paradigm shift in glaucoma management, emphasizing the need for a holistic approach targeting both IOP and neuro-protection to preserve vision effectively.

Key words: retinal ganglion cells, oxidative stress, axonal regeneration, neurotrophic.

Introduction

Glaucoma is a condition where the retinal ganglion cells degenerate, leading to vision loss. Approximately 66.8 million people worldwide are impacted by this, and this number is projected to rise to 76 million by 2020.[1] Open-angle glaucoma is the most common form and is associated with raised intraocular pressure. Although lowering intraocular pressure is effective in slowing the progression of the disease, many patients still progress to blindness. Measures to protect the optic nerve and prevent further progression of glaucoma are needed. The optic nerve suffers damage through mechanical damage at the optic nerve head and axonal injury during elevated intraocular pressure states. Ischemia due to reduced blood flow to the optic nerve head and adjacent retina is also a cause. However, other types of damage may also occur such as excitotoxicity and oxidative damage of retinal ganglion cells, these are becoming increasing areas of interest as they may be points at which neuroprotection strategies can intervene in order to prevent further progression of the disease.[2]

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2. Rodríguez Villanueva, J., Martín Esteban, J., Rodríguez Villanueva, L.J., Retinal Cell Protection in Ocular Excitotoxicity Diseases. Possible Alternatives Offered by Microparticulate Drug Delivery Systems and Future Prospects. Pharmaceutics. 2020; 24:12(2):94.

Overview of Glaucoma

Glaucoma is a group of optic neuropathies that cause degeneration of neural tissues in the retina, leading to visual field defects. Primary open-angle glaucoma (POAG) is the most common form and was previously thought to be solely dependent on intraocular pressure (IOP), but damage can occur even at normal IOP levels. Secondary forms are caused by identifiable insults to the eye. Glaucoma is an eye disease that is the leading cause of irreversible blindness around the world. POAG is more prevalent in individuals of African ethnicity, those with a family history of the disease, diabetics, severely myopic individuals, and people of advanced age.[3]

Pathophysiology Of Glaucoma

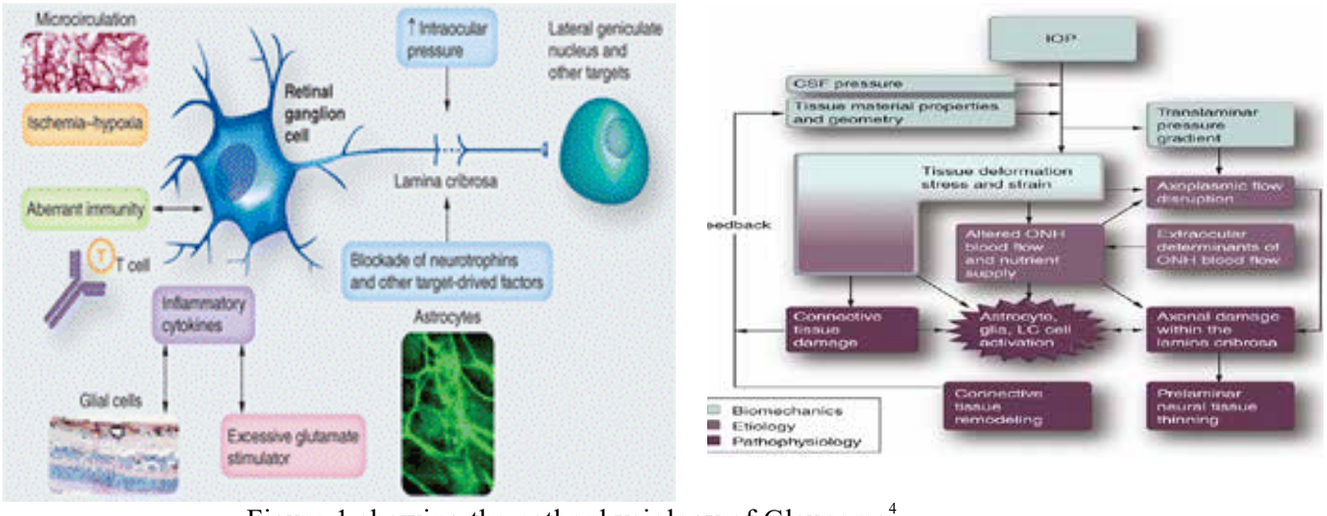

Figure 1 showing the pathophysiology of Glaucoma[4]

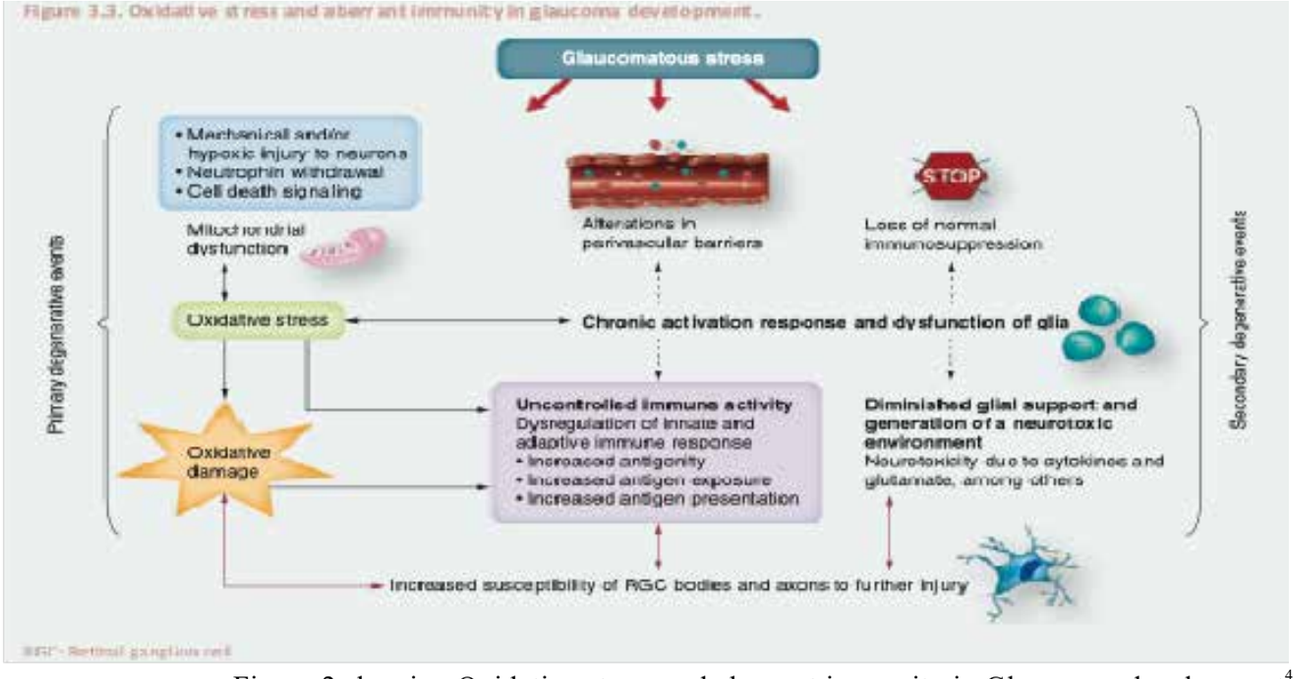

Figure 2 showing Oxidative stress and aberrant immunity in Glaucoma development[4]

3. O'Brien, J.M., Salowe, R.J., Fertig, R., Salinas, J., Pistilli, M., Sankar, P.S., Miller-Ellis, E., Lehman, A., Murphy, W.H.A., Homsher, M., Gordon, K., Ying, G.S., Family History in the Primary Open-Angle African American Glaucoma Genetics Study Cohort. American Journal of Ophthalmology, 2018, 192: 239–247. https://doi.org/10.1016/j.ajo.2018.03.014
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Importance Of Neuro-Protection In Glaucoma

It is well established that glaucoma damages retinal ganglion cells (RGCs) and their axons,[5] this damage leads to apoptosis and progressive loss of vision. There are various points at which intervention might preserve vision in patients attending the clinic with glaucoma, these include protection of the optic nerve head (ONH) and RGCs from elevated IOP, and direct neuroprotection of RGCs from apoptotic stimuli. Of these, the most widely researched target is IOP, reduction of which is proven to be effective in preventing onset and progression of the disease.[5] However, many patients continue to suffer deterioration in vision and quality of life in spite of apparently successful lowering of IOP. This suggests that damage to RGCs may not be entirely mediated by pressure, so further strategies to protect the eye and particularly the optic nerve are required. This is supported by evidence that neuroprotection by drugs, electrical stimulation and gene therapy can prevent apoptosis of retinal neurons in animal models of glaucoma, regardless of IOP level. An example of this is the recent discovery that blockade of N-methyl-D-aspartate (NMDA) receptors in the retina can prevent loss of RGCs in a rat glaucoma model.[6]

Current Neuro-Protection Strategies

Glaucoma is a disease that causes progressive damage to the optic nerve and loss of the visual field. Though treatment primarily focuses on reducing intraocular pressure, other factors may contribute to the disease. Neuroprotection is an important strategy for treating glaucoma, and this paper will review various methods to prevent further vision loss. While many neuroprotective agents are still in preclinical development, there is hope for discovering a neuroprotective regimen in the near future.

Medications/Interventions For Neuro-Protection

Lowering intraocular pressure is the only proven method to reduce glaucoma progression and determine medication licensing. Neuro-protective qualities are a significant bonus. Medications are evaluated for their ability to protect retinal ganglion cells by preventing damage and providing disease modification. Ideal medications selectively prevent damage, are neuro-protective, and may prevent nerve cell death, increase optic nerve resistance, or reduce nerve cell damage. Various tests are used to assess disease progression.

There are currently several categories of medications used in the treatment of glaucoma, and attention studies are ongoing to determine the extent of their neuro-protective effects. The potential benefit of many of these agents lies not only in their neuro-protective properties, but also in their mutual ability to lower intraocular pressure.[7]

Calcium Channel Blockers

Calcium channel blockers have been studied for their neuro-protective effects on retinal ganglion cells in response to high intraocular pressure. These blockers are commonly used to treat cardiovascular

5. Kass, M.A. Heuer, D.K., Higginbotham, E.J., Johnson, C.A., Keltner, J.L., Miller, J.P., Parrish, R.K., Wilson, M.R., Gordon, M.O.A., 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(6):701-13; discussion 829-30. doi: 10.1001/archopht.120.6.701.
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7. He, S., Stankowska, D.L., Ellis, D.Z., Krishnamoorthy, R.R., & Yorio, T. Targets of Neuroprotection in Glaucoma. Journal of Ocular Pharmacology and Therapeutics: the official journal of the Association for Ocular Pharmacology and Therapeutics, 2018; 34(1-2): 85–106. https://doi.org/10.1089/jop.2017.0041

and cerebrovascular disease, and studies suggest that individuals taking them may be less likely to experience visual field progression associated with glaucoma. However, clinical trials on the use of calcium channel blockers in the treatment of glaucoma have resulted in equivocal findings.[8]

Brimonidine

Brimonidine is an alpha-2 adrenergic agonist commonly used as an anti-glaucoma, IOP-lowering agent. Previous studies[9] using animal models have shown enhanced survival of retinal ganglion cells (RGCs) independently of IOP. Brimonidine also protects RGCs from somatic, axonal, and dendritic degeneration in optic injuries involving ischemia, NMDA-induced neurotoxicity, ocular hypertension, optic crush, and optic neuritis.[9]

Various mechanisms for brimonidine's neuroprotective effects have been purported including neurotrophic factor activation, vaso modulation, glutamate inhibition, and cell-survival signal upregulation as well as apoptosis downregulation. Specifically, brimonidine increases the transcription of neurotrophic factors (e.g. brain-derived neurotrophic factor (BDNF) and fibroblast growth factor (FGF)) and their receptors (TrkB for BDNF and FGF receptor), which regulate various cellular functions including neuronal growth, plasticity, differentiation, and survival. Brimonidine has been shown to not only protect the retina from ischemic damage in a dose- and time-dependent manner, but also to support neural regeneration after injury.[10]

Ginkgo Biloba

Ginkgo biloba has complex and multi-factorial mechanisms of action in neuroprotection. It acts as an antioxidant, reduces inflammation, and has effects on neural function. It scavenges reactive oxygen species (ROS) and inhibits ROS-producing enzymes. The terpene trilactones in Ginkgo biloba increase the activity of the antioxidant enzyme superoxide dismutase (SOD) in mitochondria. Ginkgo biloba also reduces the production of nitric oxide (NO) and inhibits lipid peroxidation. In animal models, Ginkgo biloba extract increases the activity of SOD, catalase, and glutathione peroxidase, protecting against glaucoma.[11]

Ginkgo may help to reduce oxidative stress and prevent cell death in the central nervous system. It can protect mitochondria from damage and increase blood flow to the optic nerve head, preventing damage due to hypoxia and helping with ocular perfusion pressure. Ginkgo's neuroprotective mechanisms can prevent retinal ganglion cell death and potentially delay retinal damage in glaucoma patients.[12,13]

Rho-Kinase Inhibitors

The need for an IOP-independent neuroprotective agent in glaucoma has prompted investigation of Rho-kinase inhibitors. Rho-kinase activity is increased in glaucoma, leading to various effects

8. Tsuruga, H., Murata, H., Araie, M., & Aihara, M. Neuroprotective effect of the calcium channel blocker nilvadipine on retinal ganglion cell death in a mouse ocular hypertension model. Heliyon, 2023; 9(3): e13812. https://doi.org/10.1016/j.heliyon.2023.e13812
9. Conti, F., Romano, G. L., Eandi, C. M., Toro, M. D., Rejdak, R., Di Benedetto, G., Lazzara, F., Bernardini, R., Drago, F., Cantarella, G., & Bucolo, C. Brimonidine is Neuroprotective in Animal Paradigm of Retinal Ganglion Cell Damage. Frontiers in pharmacology, 2021. 12, 705405. https://doi.org/10.3389/fphar.2021.705405
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12. Cybulska-Heinrich, A. K., Mozaffarieh, M., & Flammer, J. Ginkgo biloba: an adjuvant therapy for progressive normal and high-tension glaucoma. Molecular vision, 2012; 18: 390–402.
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on outflow resistance. Inhibition of Rho-kinase activity shows promising potential in neural tissue protection. Y-27632 is the first successfully synthesized Rho-kinase inhibitor. It competes with ATP and shuts off Rho-kinase activity. The specificity of Rho-kinase inhibitors is important due to Rho's role in various cellular functions.[14]

Rho-kinase inhibitors are a promising new area of research for treating glaucoma. They improve outflow facility in glaucomatous eyes by addressing actin cytoskeletal structures in TM cells. These inhibitors have shown a 30-50% increase in outflow facility in monkeys without any morphological changes[14]. Rho-kinase inhibitors also have a neuroprotective effect on the optic nerve by preserving axonal structures of retinal ganglion cells. This is highly advantageous as prevention of progression of visual field loss is seen as an important way of preserving the patient's quality of life. Rho-kinase inhibitors may make a significant contribution to the treatment of glaucoma in the future.[14]

Antioxidants

The most studied antioxidants in glaucoma are vitamin C, vitamin E, and glutathione. They can delay, prevent, or repair damage caused by reactive oxygen species (ROS). Vitamin C is a water-soluble scavenger of ROS and can protect lipid phase antioxidants and omega-3 fatty acids. Vitamin E is a fat-soluble antioxidant that can block apoptotic cell death in retinal ganglion cells. Glutathione is the most important antioxidant in the eye, involved in detoxification and maintaining the cell's reducing environment. Oxidative stress and decreased antioxidant defences occur in patients with primary open-angle glaucoma. The high oxygen consumption and low defence levels in the retina make it susceptible to oxidative damage from ROS production.[15]

Role of Antioxidants in Neuroprotection

Antioxidants neutralize reactive oxygen species, protecting retinal ganglion cells from apoptosis. Brain-derived neurotrophic factor (BDNF) injection upregulates antioxidant enzymes, providing significant cell death protection. Alpha lipoic acid protects retinal neurons from apoptosis and lowers intraocular pressure, it spares retinal neurons in an animal model of ischemia reperfusion injury, confirmed by immunohistochemistry. This research is significant for various neuronal injury models and human clinical trials for diseases like Alzheimer's and Multiple Sclerosis.[16]

The study of antioxidants in glaucoma has seen significant growth, with various animal models showing promise in preventing damage to retinal ganglion cells. The duration of antioxidant treatment has been found to impact its effectiveness, as demonstrated in multiple studies.[17]

Surgical Interventions For Neuro-Protection

Surgical interventions have been effective in preserving neuroretinal function in glaucoma patients. They protect the optic nerve by lowering the intraocular pressure (IOP), however, other risk factors for glaucoma damage exist, and not all

14. Pinazo-Duran, M. D., Shoaie-Nia, K., Zanon-Moreno, V., Sanz-Gonzalez, S. M., Del Castillo, J. B., & Garcia-Medina, J. J. Strategies to Reduce Oxidative Stress in Glaucoma Patients. Current neuropharmacology, 2018; 16(7): 903–918. https://doi.org/10.2174/1570159X15666170705101910
15. Candelario-Jalil, E. González-Falcón, A. García-Cabrera, M. León, O.S., Fiebich, B.L. Wide therapeutic time window for nimesulide neuroprotection in a model of transient focal cerebral ischemia in the rat. Brain Research. 2004; 1007(1–2): 98–108.
16. Pinazo-Duran, M. D., Shoaie-Nia, K., Zanon-Moreno, V., Sanz-Gonzalez, S. M., Del Castillo, J. B., & Garcia-Medina, J. J. Strategies to Reduce Oxidative Stress in Glaucoma Patients. Current neuropharmacology, 2018; 16(7): 903–918. https://doi.org/10.2174/1570159X15666170705101910
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patients with high IOP will develop progressive disease. Therefore, it is crucial to take into account the general theory and specific risk factors for the progression of glaucoma when determining which patients are benefiting from surgery.

The Ocular Hypertension Treatment Study confirmed that lowering IOP with topical medication reduces the risk of developing glaucoma in ocular hypertensive patients. The neuroprotective effects of these medications are partially independent of their IOP lowering effect. Low dose brain penetrant beta blockers are no more effective for controlling IOP than other forms of beta blockers, but their efficacy is partly due to neuroprotection. Surgical intervention for neuroprotection is currently recommended for glaucoma patients who have already had structural damage to their optic nerve[18]

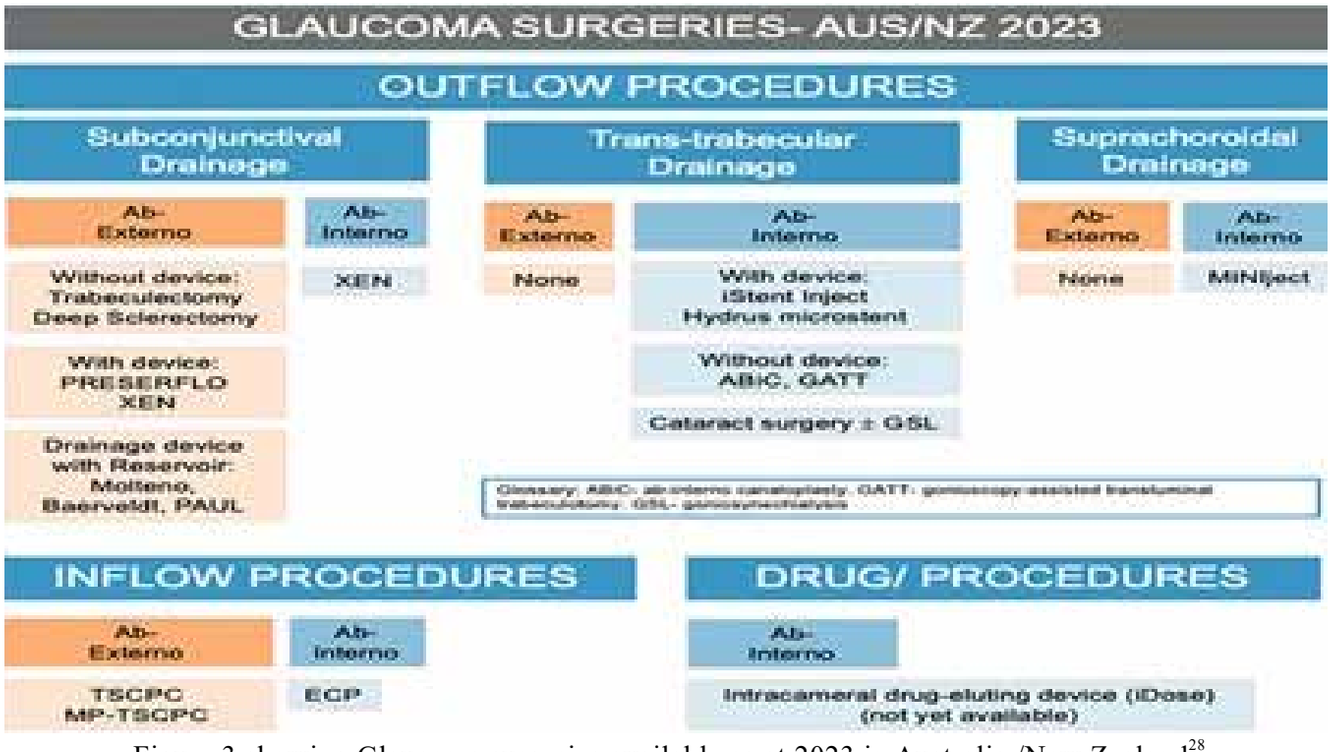

Figure 3 showing Glaucoma surgeries available as at 2023 in Australia /New Zealand[28]

Lifestyle Modifications For Neuro-Protection

Lifestyle modifications are changes in habits, activities, and diets that can positively affect overall health. Elevated IOP, atherosclerosis, and reduced ocular perfusion pressure are some of the lifestyle factors linked to the progression of glaucoma. Studies[30] suggest that a diet low in saturated fats and caffeine intake can lower IOP and reduce the risk of glaucoma. Structured exercise not only lowers systemic blood pressure but also lowers IOP. Walking for 3+ hours per week is linked to a lower risk of open angle. Glaucoma (OAG). Exercise lowers aqueous production by decreasing blood flow to the ciliary body and iris. There is a short-term increase in aqueous outflow facility after intense exercise.[29]

18. Doozandeh, A., & Yazdani, S. Neuroprotection in Glaucoma. Journal of ophthalmic & vision research, 2016; 11(2): 209–220. https://doi.org/10.4103/2008-322X.183923
28. Lim, R. The surgical management of glaucoma: A review. Clinical Exper Ophthalmology [Internet]. 2022; 50(2):213–31. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ceo.14028
29. Yuan, Y., Lin, T. P. H., Gao, K., Zhou, R., Radke, N. V., Lam, D. S. C., & Zhang, X. Aerobic exercise reduces intraocular pressure and expands Schlemm's canal dimensions in healthy and primary open-angle glaucoma eyes. Indian journal of ophthalmology.2021; 69(5): 1127–1134. https://doi.org/10.4103/ijo.IJO_2858_20
30. Al Owaifeer, A. M., & Al Taisan, A. A. The Role of Diet in Glaucoma: A Review of the Current Evidence. Ophthalmology and therapy. 2018; 7(1): 19–31. https://doi.org/10.1007/s40123-018-0120-3

Emerging Trends In Neuro-Protection

New treatments for glaucoma are aimed at protecting retinal ganglion cells (RGCs) from damage. Nitric oxide has a dual role in RGC death, and inhibiting its production could preserve surviving RGCs. Four emerging trends in neuroprotection for glaucoma are: novel drug therapies, gene therapy, stem cell therapy, and nanotechnology. These technologies show promising results and may become essential in the future management of glaucoma.

Novel Drug Therapies

Glaucoma causes progressive damage to the optic nerve, resulting in cell death and visual loss. Recent research has been focused on drugs that can protect nerves in the eye affected by glaucoma. These drugs can be systemic or local. Memantine and the μ enhancer are systemic drugs that have shown potential to protect retinal ganglion cells (RGCs) from damage,[19] Coenzyme Q10 and idebenone, which is a short analogue of CoQ10, have also been found to prevent RGC apoptosis[20]. While idebenone[20] has been found to be an ideal candidate for systemic administration, most research has been focused on locally delivered drugs to maximize the concentration of the drug reaching the target tissue while reducing systemic side effects[20]

Gene Therapy For Neuro-Protection

Gene therapy, which transfers genetic material into cells to prevent or treat a disease, has potential for treating glaucoma. The primary objective of neuroprotection is to delay vision loss and maintain existing vision. Gene therapy for neuroprotection is a promising area with recent advancements in ophthalmology has made progress in the USA.

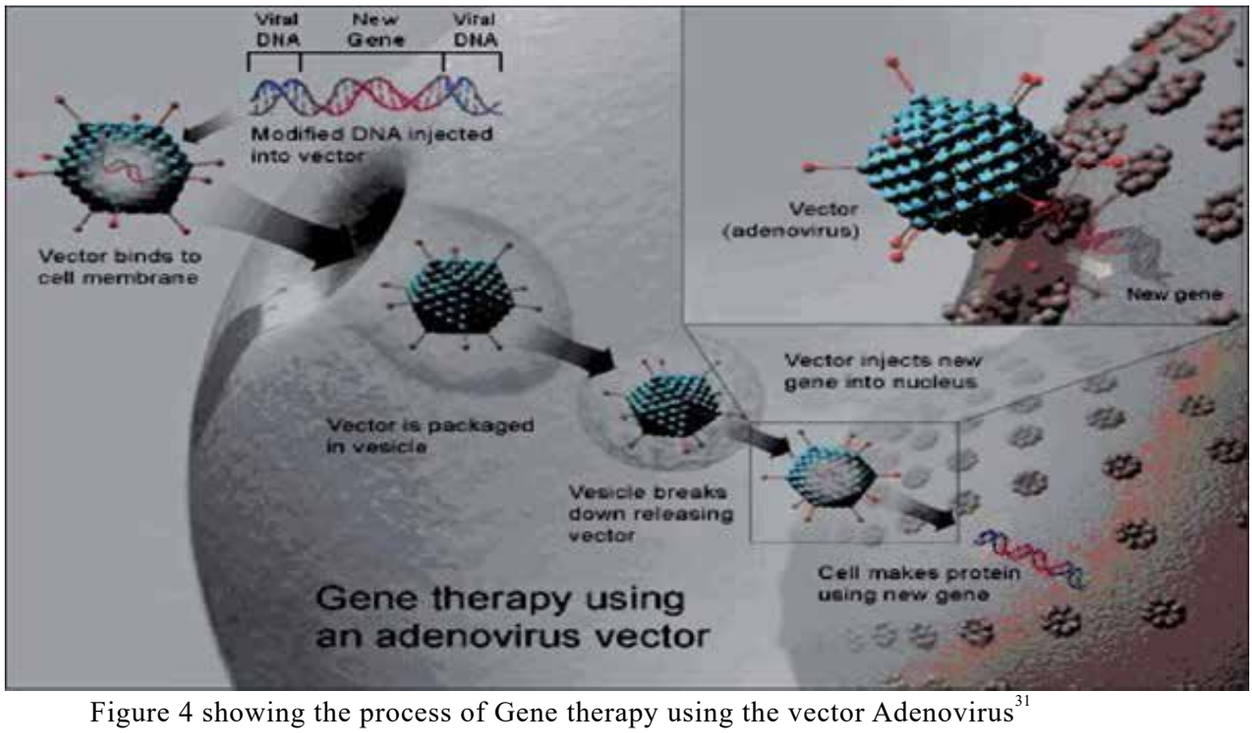

Figure 4 showing the process of Gene therapy using the vector Adenovirus[31]

19. Lipton, S. A. Possible role for memantine in protecting retinal ganglion cells from glaucomatous damage. Survey of ophthalmology, 2003; 48 Suppl 1, S38–S46. https://doi.org/10.1016/s0039-6257(03)00008-0
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Stem Cell Therapy For Neuro-Protection

The general approach to stem cell therapy is to replace damaged neurons with healthy neurons differentiated from stem cells, which have been manipulated in vitro. This is not feasible for glaucoma as the damaged retinal ganglion cells cannot be isolated and identified readily in vitro, and there is no method for introducing new retinal ganglion cells into their specific location in the retina. An alternative approach is to transplant healthy stem cells or cells differentiated from stem cells, which release neurotrophic factors. This has potential for glaucoma as there are numerous types of cells, which are known to release a variety of different neurotrophic and survival factors for retinal ganglion cells.

Retina is an ideal part of the central nervous system for stem cell therapy. An emerging trend in neuro-protection is the utilization of stem cells to restore and maintain retinal ganglion cells, which are doomed to die. This death of retinal ganglion cells in glaucoma is an important cause of blindness for which there is no current treatment to prevent or undo. If a stem cell therapy were to save or restore retinal ganglion cells in glaucoma patients, it could revolutionize the management of this common and devastating optic neuropathy[21].

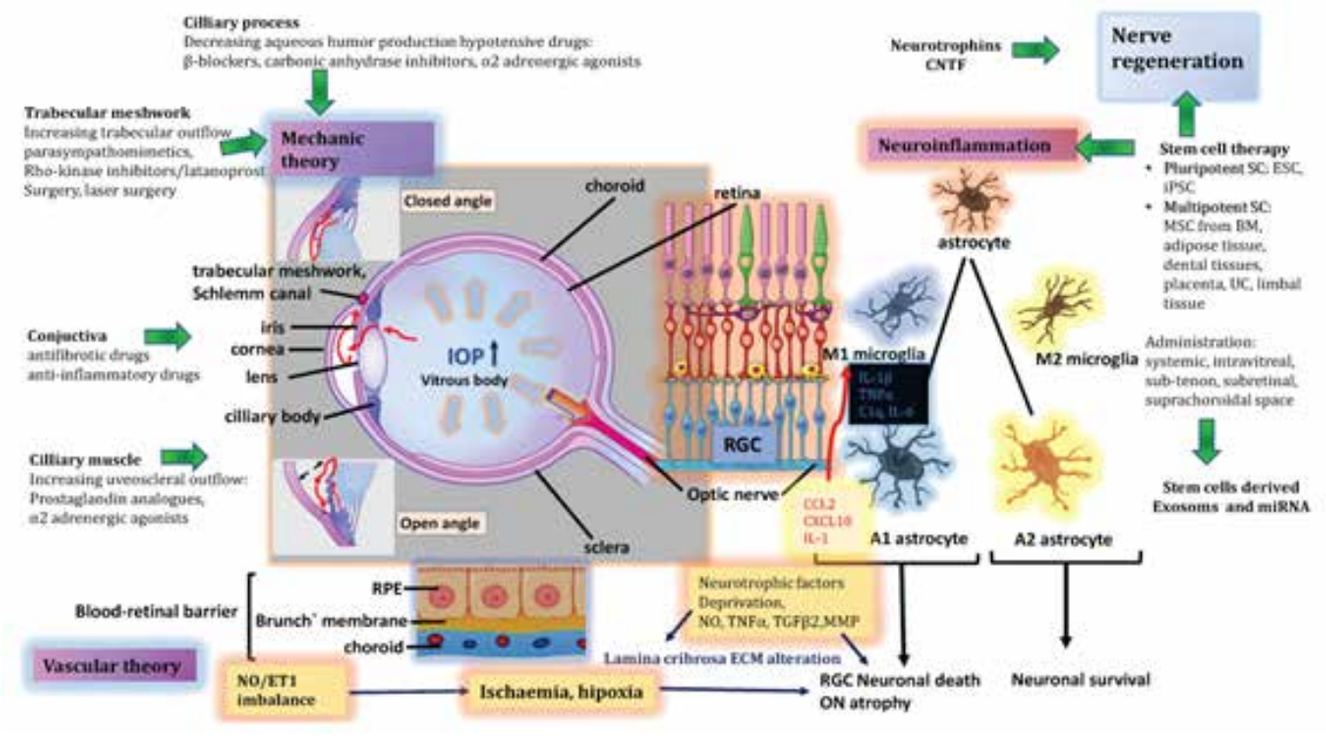
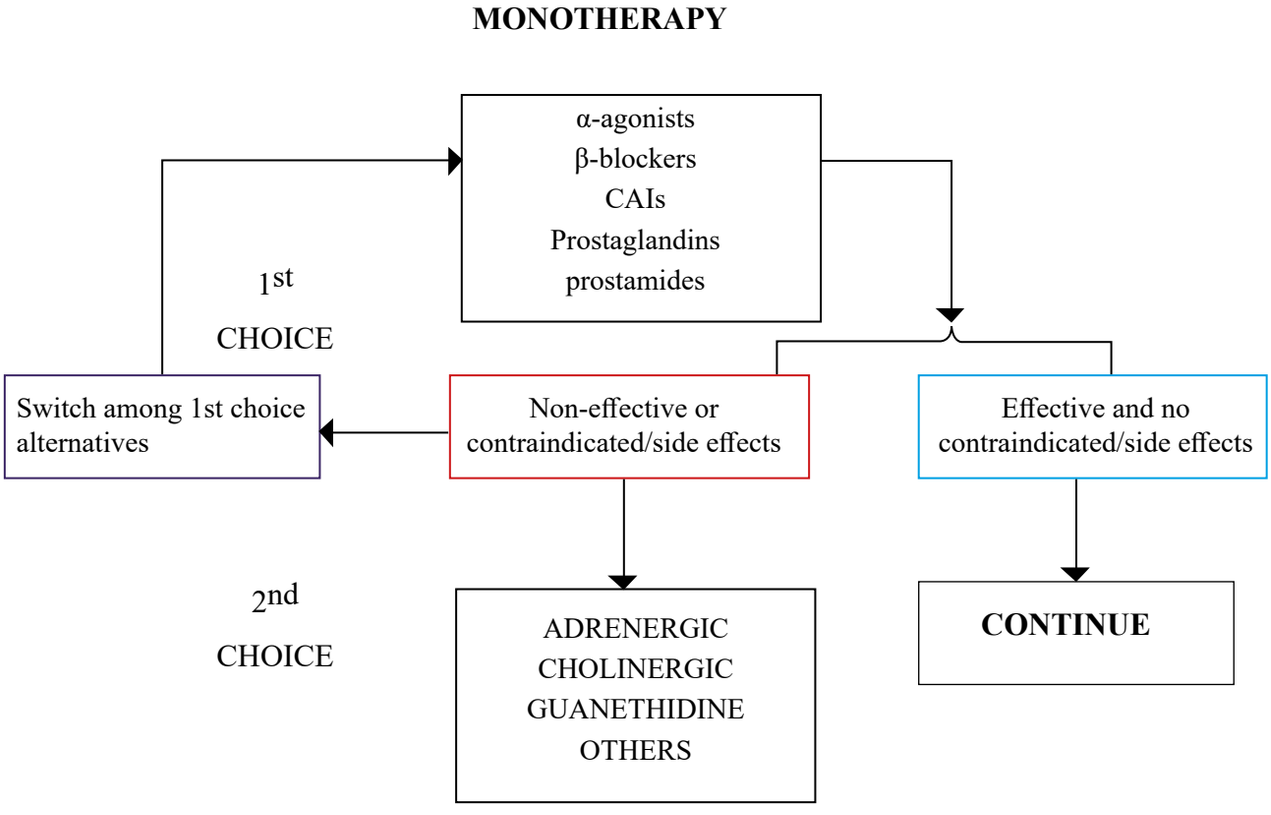


Figure 5 showing the various stem cell therapy processes[21]

21. Nicoară, S. D., Brie, I., Jurj, A., & Sorițău, O. The Future of Stem Cells and Their Derivates in the Treatment of Glaucoma. A Critical Point of View. International Journal of Molecular Sciences, 2021; 22(20). https://doi.org/10.3390/ijms222011077

Combination Therapies



α-agonists, LATANOPROST and TRAVOPROST are approved by the regulatory bodies as first-line treatment; an application has also been made for BIMATOPROST

See flowchart from European Glaucoma society

Figure 6 showing the combination therapies available for Glaucoma, (The European Glaucoma Society's recommendations on the use of monotherapy in the management of glaucoma. (Reproduced with permission from the European Glaucoma Society) [22]

For Glaucoma management various medications and laser interventions are available for treatment. While initial treatments can stabilize visual fields, some patients still experience vision loss, especially those with advanced disease, African Americans and Latinos, pseudo exfoliation glaucoma patients, and those with a positive family history. Studies suggest that pseudo exfoliation glaucoma patients may have poor outcomes with primary glaucoma surgery and may require alternative management. Recent research shows that lowering IOP can significantly delay the onset of glaucomatous damage.[23]
Combination therapy aims to achieve a 1mmHg reduction in IOP above monotherapy. Evidence

22. European Glaucoma Society. II Edition: Terminology andGuidelines for Glaucoma. Dogma Editrice:Savona, Italy; 2003
23. Holló, G., Katsanos, A., & Konstas, A. G. Management of exfoliative glaucoma: challenges and solutions. Clinical ophthalmology (Auckland, N.Z.), 2015; 9: 907–919. https://doi.org/10.2147/OPTH.S77570

suggests a 10% reduction in IOP can decrease progression rates by 40%. Treatment escalation is recommended with each stage of glaucoma. Randomized control trials and meta-analyses support the use of fixed combinations for improved patient compliance[24]. Results show an additional 1.5-4mmHg reduction in IOP.[24] Combination therapy is effective in managing IOP and minimizing ocular surface damage. It is more effective than starting with 2 agents simultaneously.[24]

Fixed combination drugs simplify dosing, improve patient compliance, and are more effective than unfixed counterparts. However, they are more expensive and may have more side effects. Topical monotherapy is the standard initial treatment, but if it fails, maximally tolerated medical therapy can be used.

Nanotechnology In Neuro-Protection

Nanotechnology is revolutionizing drug delivery to the eye, which has been a challenge due to the eye's anatomy and physiology. Gold nanoparticles are being used to study the movement of toxins in the eye related to glaucoma, potentially leading to new drug targets. Nanotechnology can create unique materials with enhanced penetration and retention properties, providing a new paradigm in medicine known as nanomedicine.[25]

Future Directions And Challenges

Neuro-protective strategies face challenges due to limited regenerative capacity of the central nervous system. Blocking RGC cell body apoptosis may not prevent axon loss and irreversible vision loss. To promote optic nerve axon regeneration, removing molecular inhibitors of neurite outgrowth is important. Scar tissue amplifies myelin inhibitors' effects on axons and leads to chronic microglial activation, which is detrimental to neuronal survival. Modulating microglial activation is a potential research area to prevent nerve damage progression. Success would bring neuro-protection closer to reality. However, this research will require further investment of time and resources. A priori, translation of new neuro-protective therapies from the laboratory into the glaucoma patient will require evidence of prevention of vision loss in human subjects, to supplement evidence of prevention of RGC death provided by visual field and/or OCT testing in clinical trials. Since these structural and functional tests can show excellent sensitivity in detecting progression of disease, trials of neuro-protection in glaucoma should theoretically be of much smaller size and shorter duration than those of new treatments for other neurodegenerative conditions where trials of several years and involving hundreds or thousands of patients may be typical. Unfortunately, given the complexity of glaucoma and likelihood of co-existing ocular and systemic disease in many patients, obtaining clear evidence of prevention of vision loss by neuro-protective therapy may be difficult. An adaptive statistical design which allows modification of the inclusion criteria and outcome measurements in response to emerging trial data may aid the best use of resources in addressing this problem[32].

24. Michelessi, M., Lindsley, K., Yu, T., & Li, T. Combination medical treatment for primary open angle glaucoma and ocular hypertension: a network meta-analysis. The Cochrane Database of Systematic Reviews, 2018(5), CD011366. https://doi.org/10.1002/14651858.CD011366.pub2
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Potential Limitations Of Neuro-Protection

Clinical trials for neuro-protective drugs can be costly and lengthy, making it challenging to develop new drugs. Industry-led research requires a cost-effective way to demonstrate neuro-protection. Multinational pharmaceutical companies need to invest significant amounts of money and resources to develop a new drug, with estimated costs of up to 1.3 billion dollars. Phase III trials aimed at proving neuro-protection are risky and costly, but necessary to achieve a change in clinical practice. The duration of clinical trials is also a significant consideration, and structural endpoints may require lengthy trial periods[26].

Detecting progression of glaucomatous neuro-degeneration through clinical methods has proven difficult. Most neuro-protective strategies aim to prevent further vision loss. The primary end-point, preventing visual field loss, requires large clinical trials of extended duration to provide conclusive results. Recruiting participants with early or moderate glaucoma can be difficult. Visual field tests can show wide variability. While clinical trials utilizing objective structural measurements may demonstrate more rapid and consistent results, this technology is still in the development phase. Much of the work for neuro-protection in glaucoma is based on results seen in experimental models. Additionally, certain limitations and challenges may eventually make validation of this therapy difficult[27].

Promising Research Areas

New treatments for glaucoma are being tested, including neuroprotective agents, therapies to improve blood flow, and stem cells. Ongoing research is expected to lead to significant advances in our understanding of the disease's mechanisms. This will help develop more effective neuroprotective treatments.

Translating Research Into Clinical Practice

A potential neuro-protective therapy requires expensive and lengthy clinical trials to be made available to patients. This is a sticking point for companies with patents for the therapy, as the expenses incurred are often beyond their capacity. If the therapy manages to navigate this obstacle and gets approved by the government, it must still demonstrate safety, efficacy, and cost-effectiveness to be considered a standard treatment for glaucoma. Neuro-protective agent memantine is an example of a current therapy that has undergone successful clinical trials. There is promise that various neuro-protective therapies will become standard treatments for glaucoma with continuing research and understanding of the disease's neuro-degenerative mechanisms[27].

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