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ABSTRACT

Background: Glaucoma, globally the second most common cause of blindness and the commonest cause of preventable visual disability, is a progressive neurodegenerative disease of the retinal ganglion cells and their axons. Neuroprotection is an evolving area in the management of glaucoma. This review aims to highlight the current neuroprotective agents under investigation and the promise they hold for future management of glaucoma.

Method: The available literature on the use of Neuroprotection in Glaucoma was reviewed using available journals and internet based search engines such as pubmed and Medline. Keywords employed were Neuroprotection and Glaucoma.

Results: There is ongoing research on neuroprotective agents in management of glaucoma. A few of the currently available anti glaucoma medications also have neuroprotective functions. The mainstay of glaucoma management however remains lowering of intraocular pressure. Nigerian literature on neuroprotection was not available.

Conclusion: It has become increasingly obvious that glaucoma represents a complex multifactorial disease that produces an accelerated rate of ganglion cell atrophy related to a numerous pathogenic mechanisms that not only most certainly involve IOP, but also include defective auto regulation and ischaemia; neurotrophic factor deficiency; glutamate mediated excitotoxicity, immune related phenomenon; intracellular calcium influx and free radical damage³. IOP lowering still remains the mainstay of treatment. Neuroprotection has promise for preventing retinal cell ganglion death independent of IOP. It therefore presents an exciting development in the pursuit for a treatment modality for this debilitating disease.

Keywords: Neuroprotection; Glaucoma.

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INTRODUCTION

Currently, glaucoma is recognized as an optic neuropathy. Selective death of retinal ganglion cells (RGC) is the hallmark of glaucoma, which is also associated with

structural changes in the optic nerve head¹.

Glaucoma can also be viewed as a neurodegenerative disease that is often associated with high intraocular pressure (IOP), and in which at any time there are fibers (optic nerve axons) and cell bodies (retinal ganglion cells) that are vulnerable to degeneration and amenable to protection². Recent evidence indicates that lowering IOP does not prevent progression in all patients and that progression can continue despite effective lowering of IOP³. This was illustrated in the Advanced Glaucoma Treatment Study Trial⁴, Collaborative Normal Tension Glaucoma Study⁵ and the Early Manifest Glaucoma Study⁶.

In recent years the focus of glaucoma research has shifted toward neuroprotection, as the traditional strategies of lowering intraocular pressure have been shown to be unable to prevent progressive vision loss in some glaucoma patients^{7,8,9,10}. Most patients with elevated IOP never develop glaucoma, many patients who do not have statistically elevated pressure (low tension glaucoma) as well as many patients with controlled IOP continue to have progressive vision loss^{11,12}. These observations suggest that an IOP independent mechanism contributes to disease onset and progression^{13,14,15}.

Mechanisms of RGC Damage & Targets for Neuroprotective Agents^{1, 8,13,15,16}

The exact mechanism(s) of RGC damage in glaucoma is complex and unknown. Potential mechanisms for neuroprotection in terms of pathways initiated by mechanical or ischemic injury, or by the toxic substances liberated by the primary insult to affected cells leading to secondary degeneration and apoptotic death.

Neurotrophic Factors

A major destructive effect of increased or fluctuating IOP is deformation of the lamina cribrosa, mechanically compressing RGC axons. This reduces or blocks retrograde transport of essential neurotrophic factors such as brain-derived neurotrophic factor (BDNF), NGF, neurotrophin (NT)-3, NT-4 and NT-5, glial cell-derived neurotrophic factor, ciliary neurotrophic factor, and FGF-2, liberated by the superior colliculus and lateral geniculate body and transported to the RGC body by its axons. A lack of appropriate target-derived trophic support causes cells to undergo apoptotic degeneration. Supplementation of these neurotrophic factors has been suggested to protect neurons from such degeneration

Ischemia

Another major theory in the etiology of glaucoma is

vascular insufficiency at the optic nerve head. Arising from systemic hypotension, vasospasm or even mechanical compression of the microvasculature at the lamina cribrosa, low perfusion of the optic nerve head may cause RGC ischemia. This ischemic insult may reduce essential nutrients and substrates available for energy production in metabolically highly active neurons. Antivasospastic drugs such as calcium-channel blockers and some adrenergic antagonists have potential as neuroprotectants.

Mitochondrial Dysfunction

Increasingly, mitochondrial dysfunction is believed to contribute to the pathogenesis of neurodegenerative disorders, including glaucoma. Mitochondria are the principal organelles for a cell's energy production (ATP) via the electron transport chain. This energy drives intracellular and intercellular signaling and is vital for cellular pump function, and thus cellular integrity. Mitochondrial dysfunction induces the intrinsic apoptotic pathway by up regulation of NF- κ B and proapoptotic genes. As mitochondrial dysfunction may be triggered by aging, ischemia and/or oxidative stress, novel methods such as caloric restriction (to try to retard aging), increasing optic head flow dynamics (with vasodilators) and decreasing oxidative stress (with antioxidants) may prove to be useful neuroprotective strategies

Glutamate Excitotoxicity

Any hypoxic environment critically drops ATP production with failure of the vital sodium/potassium pump of both neurons and their supporting glia. Membranes depolarize with increased release and reduced clearance of glutamate by dying RGCs or by metabolically compromised glial cells. As an essential CNS neurotransmitter and the main excitatory retinal neurotransmitter, glutamate is tightly regulated in the presynaptic cells; excessive levels of glutamate are toxic not only to RGCs, but also to neighbouring healthy neurons. Excessive glutamate causes calcium influx through hyperactivation of the N-methyl-D-aspartate (NMDA) receptor in a process termed excitotoxicity. NMDA receptor antagonists and some calcium-channel blockers may stabilize glutamate levels and prevent such cellular injury.

Oxidative Stress

Overstimulation of NMDA receptors also activates nitric oxide synthase (NOS), resulting in nitric oxide (NO) production. NO is a neuronal messenger critical for normal retinal neurotransmission and phototransduction. Unregulated, it has the potential to react with the superoxide anion to form peroxynitrite, a highly reactive oxidant species. Oxidative stress is the leading cause of RGC loss, causing secondary degeneration to adjacent neurons either by direct neurotoxic insult through free-radical damage of cell membranes, enzymes, proteins and DNA; or indirectly through induction of glial dysfunction and activation of apoptotic pathways through its detrimental action on mitochondrial energy production. A wide variety of free-radical scavengers and NOS inhibitors are being investigated as potential therapeutic agents.

Protein Misfolding

Misfolded proteins such as amyloid (A β) are a prominent

feature of many neurodegenerative diseases, including Alzheimer's, Huntington's and Parkinson's, with an accumulation of abnormal protein plaques in the brain. A β has been linked to glaucomatous RGC apoptosis in a dose- and time-dependent manner, targeting different components of the A β formation and aggregation pathways (e.g., using A β antibodies) may effectively reduce glaucomatous RGC apoptosis.

Heat-shock proteins (Hsps) are chaperone proteins that facilitate nascent and stress-induced protein folding and unfolding, and restoration of misfolded proteins. HspB1 (Hsp27) is strongly induced during the stress response and has been associated with increasing the survival of cells subjected to cytotoxic stimuli. Antibodies against Hsp27 have been identified in patients with glaucoma. It is unclear whether these autoantibodies exist as a result of RGC injury, or effect a mimicked T-cell-mediated response to RGC damage. Development of decoy antigens or vaccines may be a useful strategy for neuroprotection in glaucoma.

Glial Cell Modulation

Retinal ganglion cells are not the only cells damaged in glaucoma: Müller glial cells, amacrine and bipolar cells are also injured. In the nonmyelinated region of the optic nerve head, astrocytes are the major glial cells to provide support to neuronal axons, as well as interface between connective tissue and blood vessels. They help to maintain ion homeostasis and extracellular pH, as well as integrity of the perineural extracellular matrix. To try to maintain homeostasis, quiescent astrocytes are transformed into a reactive state by liberated cytokines such as TGF β , ciliary neurotrophic factor, GF and PDGF. Reactive astrocytes exhibit altered intercellular communication, migration, growth factor signaling, oxidative species buffering capacity and connective tissue properties at the optic nerve head. Modulation of glial cell activity may therefore be useful as neuroprotective processes in the rescue of neurons following an injurious insult.

Apoptotic Death Pathways

The final common pathway for any neuronal injury is necrosis or apoptosis, the latter playing a major role in RGC death in glaucoma. Apoptosis can be initiated by extrinsic or intrinsic pathways. Triggers for the extrinsic pathway include TNF α , Fas ligand and TNF-related apoptosis-inducing ligand. The intrinsic pathway involves mitochondrial-mediated events. Regardless of the initiating injury, there is activation of the caspase cascade, increased expression of proapoptotic genes such as Bax/Bid down regulation of antiapoptotic genes such as Bcl-2/Bcl-xl, leading to noninflammatory programmed cell death.

NEUROPROTECTIVE AGENTS^{1,3,7}

Numerous neuroprotective agents have been identified. In this section, we discuss some agents currently being explored for their neuroprotective properties.

Neurotrophic Factors

Neurotrophins, such as NGF and BDNF, have been tested in animal models of glaucoma and while some studies have shown them to reduce RGC death¹⁷.

Nerve growth factor and BDNF bind high-affinity TrkA and -B receptors selectively expressed on RGCs, as well as low-affinity p75NTR receptors on Müller cells. Strategies to overcome neurotrophin deprivation include exogenous supplementation of neurotrophins or direct activation of its receptors. Brimonidine protects against many types of ocular injury, including ischemia, compression, and transient and chronic ocular hypertension. The exact mechanism(s) are not well defined¹⁷ but include induction of FGF and BDNF synthesis¹⁸ up regulation of antiapoptotic genes such as Bcl-2 and Bcl-XL, inhibition of ischemia-induced glutamate release or perhaps NMDA receptor modulation¹⁹.

Calcium-channel Blockers

An increase in intracellular calcium is neurotoxic through activation of calcium-dependent catabolic enzymes. Calcium-channel blockers such as memantine, flupirtine and dextromethorphan reduce calcium influx by their action at the NMDA receptor¹. Other better-known calcium channel antagonists such as nifedipine, verapamil and diltiazem have also been investigated, at least in normal-tension glaucoma²⁰.

Although it remains unclear whether the activity of calcium channel blockers is mediated through direct action on calcium status or indirectly through improved optic nerve blood flow, any benefit from these calcium channel blockers must be weighed against potential detrimental effects from systemic hypotension (including nocturnal) possibly contributing to ischemic stress at the optic nerve head by reducing the optic nerve head perfusion pressure²¹.

Antioxidants/Free-radical Scavengers

Coenzyme Q10 (CoQ10) provides protection in neurodegenerative conditions such as Huntington's, Parkinson's and Alzheimer's disease. Several mechanisms of action are possible. First, as CoQ10 is an important component of the mitochondrial electron transport chain, it potentiates energy production to overcome the consequences of excessive glutamate. Second, it inhibits the transcription factor NF- κ B, responsible for inflammation and autoimmune disease. Third, it inhibits opening of the mitochondrial permeability transition pore (PTP), which is involved in cell death pathways. Finally, as a free-radical scavenger, CoQ10 prevents oxidative damage to critical cellular structures caused by oxidative stress¹.

Vitamin E (α -tocopherol) is the major source of lipid-soluble antioxidants in cells and may have vasoregulatory and protein kinase C-mediated glutamate transport activity²².

Ginkgo biloba (EGb 761) increases the survival of RGCs in experimental models. The precise mode of action of EGb 761 is not fully understood, but it has putative properties as a potent antioxidant and free-radical scavenger, nitric oxide inhibitor, vasodilator, platelet-activating factor inhibitor and glutamate NMDA receptor inhibitor. Only limited data are available to support its clinical use in glaucoma¹.

Acetylcholinesterase Inhibitor²³.

In an in vivo study, the systemic administration of galantamine, an acetylcholinesterase inhibitor, was found to

promote protection of RGC soma and axons in a rat glaucoma model. Functional deficits caused by high IOP, assessed by recording visual evoked potentials from the superior colliculus, were improved by galantamine. These effects were not related to a reduction in IOP because galantamine did not change the pressure in glaucomatous eyes and it promoted neuronal survival after optic nerve axotomy, a pressure-independent model of RGC death. These data provide the first evidence of the clinical potential of galantamine as neuroprotectant for glaucoma and other optic neuropathies, and identify muscarinic receptors as potential therapeutic targets for preventing vision loss in these blinding diseases.

Nitric Oxide Synthase Inhibitor

Aminoguanidine is a potent inhibitor of inducible NOS (NOS-2) expressed on reactive astrocytes and some microglia, but its effectiveness in animal models of glaucoma remains inconclusive.

NMDA Receptor Antagonists

Memantine, an NMDA glutamate receptor antagonist, has been the most prominent neuroprotective agent in glaucoma. It was the first drug approved for use as a neuroprotective agent in moderate-to-severe Alzheimer's dementia. It is clinically tolerable and widely available. Evidence of its usefulness in glaucoma arises from animal glaucoma models, where memantine was protective against retinal ganglion cell loss, neuronal shrinkage within the central visual pathway and loss of visual function¹.

Dextromethorphan, a weakened narcotic commonly available as an anti-tussive, has NMDA antagonist activity, and has been explored for possible neuroprotection following ischemic retinal injury¹.

Immune Mediators

Geranylgeranylacetone, an acyclic polyisoprenoid, induces up regulation of HSP-72 expression in RGCs and protects them from glaucomatous damage in a rat glaucoma model. Although unused in glaucoma patients, it warrants consideration because it is administered orally, has low toxicity and is available as an anti-ulcer drug.

Amyloid β antibodies (A β s) have been shown to reduce RGC apoptosis for up to 16 weeks after a single dose in an ocular hypertensive rat glaucoma model. A β abs may act by clearing A β deposition and blocking A β aggregation¹.

Tumor necrosis factor (TNF- α) is a critical mediator of cellular apoptosis as it induces both caspase-dependent and -independent components of the mitochondrial cell death pathway¹.

Currently available glaucoma medications with neuroprotective properties³:

CONCLUSION:

Selective death of ganglion cells is the hallmark of glaucoma^{1,3,7,9,12}. The process of cell death is thought to be biphasic: a primary injury responsible for initiation of damage followed by secondary degeneration related to noxious environment

surrounding the degenerating cells. Neuroprotection is a process that attempts to preserve cells spared during the initial insult but still vulnerable to damage². Several neuroprotective agents are still under investigation. A few antiglaucoma agents have been found to also possess neuroprotective functions³. Neuroprotection is an evolving area in the management of glaucoma. The ideal neuroprotective agent when available will be of great use in arresting the progression of glaucoma, but for now, intraocular pressure lowering still remains the main stay of treatment.

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