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Review Article

Neuroprotection in Glaucoma: A Paradigm Shift

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ABSTRACT

Glaucoma is a complex, multifactorial eye disease characterized by loss of retinal ganglion cells (RGCs) and their axons, leading to progressive, irreversible optic neuropathy and visual field loss. The weight of current clinical evidence, therefore, suggests that a novel approach, independent of intraocular pressure (IOP) lowering, aimed at protecting the retinal ganglion cells and optic nerve head from damage is most desirable. The underlying pathophysiologic basis of glaucoma may be attributed to neurodegenerative changes involving multiple pathways and diverse mechanisms. These pathways are potential targets for multifunctional drugs aimed at neuroprotection against glaucoma. The most rational therapeutic approach in reversing or preventing retinal ganglion cell death entails simultaneously targeting these multiple pathways. Hence, the idea of neuroprotection remains a novel therapeutic and promising prospect in the management of glaucoma. This review paper examines current issues on the pathophysiologic basis, potential targets and novel therapeutic approach to neuroprotection in glaucoma.

Keywords: Glaucoma, intraocular pressure (IOP), neurodegeneration, neuroprotection, retinal ganglion cells (RGCs).

INTRODUCTION

Glaucoma, a multifactorial eye disease, is the second major cause of blindness worldwide with prevalence estimated at 11.1 million by 2020[1]. It is the leading cause of irreversible blindness all over the world. It is characterized by loss of retinal ganglion cells (RGCs) and their axons leading to progressive, irreversible optic neuropathy and visual field loss. It has been demonstrated in a number of studies that disease progression in glaucoma may continue despite effective intraocular pressure (IOP) reduction [2-4]. Current clinical diagnosis of glaucoma is now predicated on recognition of neuropathy clearly defined by visual field changes and no longer on elevated levels of intraocular pressure [5-6]. Neuroprotective mechanisms protect neurons from degeneration or apoptosis, and have been applied successfully in treatment of neurodegenerative conditions such as Alzheimer’s disease, parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis and Huntington’s disease.The idea of neuroprotection in glaucoma is aimed primarily at preventing destruction of retinal ganglion cells and optic nerve fibres enhancing their survival and recovery from progressive injury. It is pertinent to note that notwithstanding the underlying pathophysiology of disease condition in glaucoma, neuroprotection may still be beneficial [7,8]. The weight of current clinical evidence, therefore, suggests that a novel approach independent of intraocular pressure lowering aimed at protecting the retinal ganglion cells and optic nerve head from damage is most desirable.

Pathophysiologic Basis and Potential Targets for Neuroprotection: A number of pathophysiologic pathways are involved in glaucoma. The precise mechanisms and sites of primary injury whether in

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the retinal ganglion cells or axons still remain in doubt? The pathophysiologic basis of glaucoma progression may be attributed to central neurodegenerative changes in the visual pathway [9]. Glaucoma like other neurodegenerative diseases is unlikely to be adequately mitigated by single drug acting on a single target or pathway, due to the complexity and heterogeneous nature of the pathogenesis of this condition [10]. The current approach to drug discovery in neurodegenerative disorders including glaucoma is the one-target, one-drug paradigm aimed at identifying a single target to which is bound a single chemical entity [11].The relevance of this paradigm has been queried in view of reports from large scale genomic studies suggesting that multifunctional drugs, directed towards several pathophysiologic mechanisms have far less limitations than drugs directed towards single target or pathway [12,13].
A significant cause of retinal ganglion cell death in glaucoma may be attributed to glutamate-mediated excitotoxicity through NMDA (N-methyl-D-aspartate) receptors [14,15]. Glutamate is an excitatory neurotransmitter in the central nervous system as well as the retina. The persistent activation of ionotropic glutamate receptors results to excitotoxic neuronal injury involving a self-perpetuating cascade of events [16].

The influx of extra-cellular calcium which acts as second messenger activating a cascade is responsible for glutamate-mediated neuronal toxicity [14]. Hence, the opening of ionic channels and influx of calcium and sodium is dependent on NMDA receptor activation. It should be noted that there is clear evidence of elevation of glutamate in the vitreous of glaucoma patients [17] which buttresses the fact that prolonged exposure or high doses of glutamate promote retinal ganglion cell death, mediated via over stimulation of ionotropic glutamate receptors [18]. High calcium level is inimical to cell survival. The dephosphorylation of the pro-apoptotic mitochondrial membrane-bound proteins is facilitated by a calcium-dependent phosphatase, calcineurin, leading to calcium-induced neuronal apoptosis. The dephosphorylation results in release of cytochrome C and eventual neuronal suicide due to binding to Bcl-2 or Bcl-X_L [19]. The controlled release of glutamate in the retina is influenced by the L-type voltage-dependent calcium channels [20].

Apoptosis may be triggered by intracellular and extracellular events including trophic factor deprivation or oxidative damage. Apoptosis is the final common pathway for neuronal damage affecting the retinal ganglion cells. Apoptosis is a process whereby the cell initiates a programmed cell death resulting in genomic fragmentation, nuclear pyknosis and cell shrinkage [21]. Whatever the inciting insult or injury, actual cell death occurs through a final common pathway. Studies have described the process of secondary degeneration wherein neuronal damage continues even when the primary cause of damage is ameliorated or eliminated. These studies also revealed that healthy neurons suffer progressive damage due to their close proximity to the dying neurons as the former are exposed to the noxious environment created by the latter and subsequently suffer the same fate of cell death. Thus, neuronal death can be thought to occur in three stages: axonal injury, death of the injured neuron, injury to and death of the neighbouring intact neurons through secondary degeneration [22].

Neurotrophins are growth factors obtained by retrograde axoplasmic transport that are known to maintain normal cellular milieu of neurons by regulating cellular metabolism [23]. Hence, retinal ganglion cells will not survive following neurotrophin withdrawal by blockade of retrograde axoplasmic transport [24, 25]. The blockade is consequent on deformation of lamina cribrosa, leading to compression of retinal ganglion cells. Neurotrophin support is provided by a group of peptides comprising nerve growth factors (NGF), brain derived neurotrophic factor (BDNF), ciliary neurotrophic factor, FGF-2 and neurotrophins-3, 4 and 5 (NTF–3, NTF–4, NTF–5). These are liberated by the superior colliculus and lateral geniculate body and transported to RGC body by their axons. A lack of target derived trophic support result in apoptotic degeneration

Retinal ganglion cells are particularly liable to oxidative stress due to the high metabolic activity of retinal tissues leading to generation of free radicals. The breakdown of protein, lipid peroxidation and nucleic acid degeneration resulting in cellular death, are consequent on free radical interference with macromolecular cellular constitutions [26]. Reactive oxygen species are not only involved in the cellular death signaling transduction pathway by acting as second messengers and/or modulating protein function by redox modifications of downstream effectors, through enzymatic oxidation of specific amino acid residues; but have direct cytotoxic effects leading to death of retinal ganglion cells [27]. Again, studies have shown that there is increased concentration of free radicals in the aqueous humour of glaucoma patients which exposes the trabecular mesh work to chronic oxidative stress. This chronic insult by free radicals compromise the trabecular mesh work. Pathogenic insults including ischemia-reperfusion, excitotoxicity and inflammation are associated with raised levels of nitric oxide in the retina leading to increased free radical activity and neuronal death of retinal ganglion cells [28,29]. The optic neuropathy associated with glaucoma, in which the reactive astrocytes and microglia in the optic nerve heads are implicated, is reported to be associated with excessive nitric oxide [30,31]. Nitric oxide is believed to play a major role in the pathophysiology of several neurodegenerative conditions including glaucoma [32]. Nitric oxide synthase is responsible for generation of nitric oxide and the neuronal form of nitric oxide synthase was shown to be significantly elevated in a rat model of glaucoma [33].

The accumulation of abnormal protein plaques is a feature of neurodegenerative diseases. Amyloid β peptide known to be involved in the pathogenesis of Alzheimer's disease has been implicated in inducing the apoptosis of retinal ganglion cells *in vivo* in glaucoma [34,35]. The elevation of endothelin-1 levels, a potent vasoconstrictor in the aqueous humour and plasma, compromises blood supply to vascular tissue leading to vascular insufficiency [36]. The release of tumor necrosis factor alpha (TNF-α) by astrocytes and microglia, leading indirectly via caspase-8 to apoptosis, is as a result of the ischemic insult. Astrocytes play a crucial role in providing support to the neuronal axons maintaining extracellular pH and integrity of the perineural extracellular matrix.

Heat shock proteins, known to play a crucial role in normal physiological function, are highly expressed in glaucoma, and believed to be a form of endogenous defense mechanism. However, evidence suggests that they may trigger immune response leading to disease progression in glaucoma [37]. Heat shock proteins have been shown to be implicated in mechanisms that trigger the apoptotic cascade in glaucoma [38].

NOVEL THERAPEUTIC APPROACH TO NEUROPROTECTION

The use of NMDA receptor antagonist is a potentially effective strategy for preventing retinal ganglion cell loss by reducing excessive glutamate levels, thereby reducing NMDA receptor overactivity and excitotoxicity[18]. MK-801 was considered inappropriate for clinical use due to complete blockade of glutamatergic neurotransmission in an experimental model of glaucoma [39]. Memantine, NMDA receptor blocker approved for use in Alzheimer's disease and vascular dementia has been shown to be very effective neuroprotectant in animal model of glaucoma [40]. Regrettably, a recent large-scale randomized phase 3 clinical trial on neuroprotection in respect of memantine failed to meet the primary endpoint [41] and did not exhibit significant efficacy in preservation of visual function [42]. Similarly, eliprodil, newer NMDA receptor antagonist, has shown promising results in animal studies, however, clinical trials have not been undertaken for glaucoma in humans.

Calcium channel blockers, such as amlodipine, nifedipine and verapamil by increasing blood flow to the retinal ganglion cells may influence neuroprotection [43]. They exert effect on NMDA receptor [7] and improved homeostasis in the optic nerve head by enhancing glutamate metabolism [44]. However, the systemic hypotension associated with calcium channel blockers may lead to reduction in perfusion pressure, further worsening retinal ischemia, and contributing to ischemic stress at the optic nerve head.

Antiapoptotic agents, such as brimonidine activates extracellular signal regulated kinase (ERK) which in turn enhance the production of Bcl-2 and Bcl-X_L[45].The blockade of apoptotic pathway can be effected using caspase inhibitors. The caspase inhibitor, calpeptin has been shown to enhance neuroprotection in experimental models of glaucoma [46]. Brain-derived neurotrophic factors (BDNF) and ciliary neurotrophic factor (CNTF) have been shown to improve survival of retinal ganglion cells following optic nerve injuries[47,48].The combination of a CNS-specific leucine-rich protein (LINGO-1) antagonist with BDNF is known to improve long term viability and survival of retinal ganglion cells. A study revealed that neurotrophins decreased retinal ganglion cell death in animal models of glaucoma [49]. Neurotrophic factors such as BDNF and NGF are known to bind high affinity Trk A and B receptors expressed on retinal ganglion cells, as well as low affinity p75NTR receptors.

Antioxidants and free radical scavengers such as superoxide dismutase, catalase, vitamins C and E (tocopherol) may reduce retinal ganglion cell death [50]. The vasoregulatory and protein kinase C-mediated glutamate transport activity of tocopherol (vitamin E) has been demonstrated in animal model of ischemia-reperfusion injury [51]. Coenzyme Q10 is a free radical scavenger known to be effective in glaucoma as well as other neurodegenerative conditions. It enhances energy production being an essential component of mitochondrial electron transport chain, inhibits the principal inflammatory mediator, nuclear factor kappa B (NF-KB) and mitigates oxidative stress induced cellular injury. Ginkgo biloba (EGb761), apart from its free radical scavenger characteristic, may exert multifactorial mechanisms, which include increased ocular blood flow to optic nerve head [52], enhancing ATP production and preservation of mitochondrial metabolism. Others include, nitric oxide inhibition and improvement of cognitive function due to improved cerebral blood flow [53].

Drug targets directed towards amyloid β peptide may provide a potential therapeutic approach for glaucoma treatment. Hence, progressive glaucomatous damage may be effectively decreased by targeting different components of antibody formation and aggregation pathways. Heat shock proteins, otherwise known as stress proteins, are highly expressed in glaucoma and believed to account for endogenous defense against trauma, though evidence has shown that they may later contribute to disease progression by activating immune responses [37]. Heat shock proteins have been linked to mechanisms initiating progressive damage to retinal ganglion cells in glaucoma, hence, providing a potential therapeutic target [38]. Geranylgeranylacetone, currently indicated for treatment of peptic ulcer disease, has been shown to evoke up-regulation of HSP-70 in retinal ganglion cells, providing potential neuroprotection against glaucomatous damage [54].

Research in Alzheimer's disease has established TNF-α as a mediator of chronic inflammation with detection of increased levels in the brain of victims of this neurodegenerative disorder [55]. Extensive research evidence support the role of TNF-α in glaucomatous optic nerve degeneration and RGC apoptosis [56]. Etanercept, a recombinant chimeric protein, is a TNF-α inhibitor which is known to reduce RGC loss in the wake of elevated TNF-α. This drug shows promise as a neuroprotective agent for intravitreal use in the future.

CONCLUSION

Glaucoma is a complex disease condition involving multiple pathophysiologic mechanisms independent of raised intraocular pressure. It is clearly evident that intraocular pressure lowering alone is insufficient in significantly reducing loss of retinal ganglion cells and reversing disease progression in glaucoma. Consequently, the idea of neuroprotection remains a novel therapeutic and promising prospect in the management of glaucoma.

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