Review Article

Management of glaucoma with neuroprotective drug

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Abstract

Glaucoma is an optic neuropathy characterized by progressive loss of retinal ganglion cells (RGCs). Death of ganglion cells is not always only pressure dependent mechanism but also have several pressure independent mechanism that establish a cascade of changes that ultimately leads to cell death.

Neuro- protection is a process that attempt to preserve the cells that were spared during initial insult, but are still vulnerable to damage. Although not yet available, a neuroprotective agent would be great use that rescue neurons already compromised or that promote regrowth of axonal or dendritic connection to restore function.

This review based on literature, giving the idea of varies mechanism of RGC death delineated by research and discussed some pharmacological agent believed to have a neuroprotective role in glaucoma.

Introduction

Glaucoma is a neurodegenerative disease in which intraocular pressure (IOP) is a leading risk factor[1,2]. Despite IOP lowering, glaucoma continues to worsen in a subset of patients[2-5]. The final stage in glaucoma involves retinal ganglion cell (RGC) damage and death[2]. This damage can occur at statistically high, average, or low levels of IOP. While the biomechanics of optic disc cupping specifically, loss of neuroretinal rim and posterior bowing of the lamina cribrosa have been extensively studied[6,7]. They do not adequately explain why certain patients continue to demonstrate worsening of the disease in spite of apparently low IOP. In addition to IOP, several other triggers are hypothesized to contribute to RGC axonal injury and death[8].

These triggers include loss of neurotrophic factors, localized ischemia, excitotoxicity, alterations in immunity, and oxidative stress. There is increasing evidence that these factors, triggered by high IOP or occurring independently of IOP, may contribute to affecting the optic nerve.

Basis of neuroprotection

Glaucoma is an axonal disease in which Retinal ganglion cell (RGC) axons are the initial site of damage. According to the biomechanical model of damage, structural failure of laminar beams and strain along the retinal nerve fiber layer lead to axonal damage. Damaged axons then degenerate via apoptosis (an energy-requiring form of cell death) either in a retrograde fashion or by Wallerian degeneration. Axonal transport is disrupted primarily at the level of the lamina cribrosa[9,10]. A decrease in the axonal blood flow follows mechanical injury and death of RGCs[9,10]. The exact pathophysiology of axonal injury and death remains unclear; however, a variety of inter and intra-cellular events are triggered during the process of cell death, and these events may be potential targets of neuroprotective strategies. In many neurologic diseases, injury can spread to connected neurons by a mechanism called transsynaptic degeneration. The surrounding axons may undergo apoptosis because of the loss of certain neurotrophic factors, such as brain-derived neurotrophic factor and nerve growth factor[11,12]. On the other hand, surrounding axons may be exposed to upregulated factors that lead to cytotoxicity, such as tumor necrosis factor-

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a (TNF-a) [13,14]. It is unclear whether the process of transsynaptic degeneration affects only surrounding RGC axons or whether afferent neurons within the inner retina may also be affected.

Inhibition of intracellular calcium ion (Ca2+) uptake has been a major focus of glaucoma neuroprotection because an increase in intracellular Ca2+ is associated with RGCs degeneration. Calcium enters cells through voltage-gated channels and N-methyl-d-aspartate (NMDA) glutamate receptor associated channels. An increase in intracellular Ca2+ activates calcineurin, Which causes the release and activation of apoptotic mediators, such as caspases from mitochondria into the cytoplasmic space[15].Cytoplasmic Ca2+ also stimulates nitric oxide production. The upstream trigger for this cascade of events may be glutamate dependent. Neuroprotection in glaucoma is the targeted treatment of neurons of the visual pathway (particularly RGCs) that are damaged in the glaucomatous process.

In neuroprotection, the goal is to directly stimulate or inhibit specific biochemical pathways that either prevent injury or stimulate recovery of these neurons. Indirect treatments, such as IOP lowering, by definition are not neuroprotection. Retinal ganglion cell njury may occur by a variety of pathophysiologic mechanisms including increased intraocular pressure, ischemia, genetic factors, and failure of trophic support. Conventional treatment to prevent optic neuropathy has focused on preventing or mitigating the effect of the inciting factor. Neuroprotection in glaucoma involves targeted modification of NMDA receptor and promotes Ca2+ uptake[16]. An increase in intravitreal glutamate causes RGC death in vitro; however, an increase in intravitreal glutamate has not been observed in experimental models of glaucoma[17]. Glutamate toxicity has also been shown to

lead to degeneration of postsynaptic neurons in the lateral geniculate nucleus[18].

Neuroprotective medications

There are several theoretically effective neuroprotective therapies that unfortunately remain somewhat limited in practice. While cell culture results with brain-derived neurotrophic factor have been promising, its effect is only transient, which may possibly be due to receptor turnover[19]. Altering the expression of apoptosis proteins is possible in transgenic animals, but it cannot be easily achieved or controlled in humans[20]. Finally, experimental models of RGCs axonal injury (cell cultures and murine or primate models) do not entirely reproduce the multifactorial pathophysiologic events of glaucoma in humans. Nevertheless, strong experimental Evidence for certain medications may lead to clinical use in the near future.

Memantine

Memantine is an NMDA receptor antagonist that blocks the excite toxic effects of glutamate[21]. The drug has been used to treat Parkinson's and Alzheimer's disease[22]. Glutamate-mediated synaptic transmission is critical for normal functioning of the nervous System; however, if neurons are injured and unable to properly control the regulation or clearance of glutamate, secondary excite toxic damage can result. Under pathologic conditions, the NMDA receptor is over activated and excessive Ca2+ influx occurs[23]. Therefore, oral Memantine theoretically may benefit patients with progressive glaucoma. Memantine has been shown to protect RGCs and brainstem neurons in a monkey model of glaucoma[24]. However, a recent report from a Phase III clinical trial indicates that Memantine failed to show efficacy compared with placebo when used in patients with glaucoma[25].Given the results of this trial, the exact role of Memantine in glaucoma patients remains unclear. We currently

counsel patients who show stereophotographic or perimetric progression of glaucoma despite maximally tolerable IOP lowering therapy about the absence of additional clinically proven therapies for glaucoma. Because of the safety profile of Memantine and its theoretical benefit in preventing axonal injury, patients in whom standard medical or surgical therapy is ineffective or not possible are offered treatment with Memantine.

Brimonidine

In addition to lowering IOP, alpha-2 adrenergic receptor agonists also increase release of neurotrophic factors, inhibit glutamate toxicity, and reduce Ca2+ uptake by neurons in both in vitro and in vivo animal models[26,27]. This class of medication may also inhibit activation of proteins involved in apoptosis[28]. Alpha-2 receptors are found in a variety of retinal locations and are expressed in RGCs[29]. Topically administered alpha-2 agonists, such as Brimonidine, have been found to achieve neuroprotective intravitreal concentrations[30]. The efficacy of Brimonidine in normal-tension glaucoma patients is currently being evaluated prospectively.

However, the neuroprotective effect of Brimonidine remains controversial given the medication's accompanying IOP-lowering effect. A clinician also cannot a priori determine whether glaucomatous damage is due to a pressure-dependent or pressure-independent process. As such, we do not use Brimonidine as a first-line treatment for glaucoma when other medications are tolerated, nor do we use Brimonidine for a neuroprotective effect. Further studies are needed to determine the utility of Brimonidine in glaucoma neuroprotection.

Betaxolol

Selective beta-1 adrenergic antagonists (Betaxolol) have a similar neuroprotective effect in vitro as the alpha-2 agonists. Betaxolol increases neurotrophin levels, decreases intracellular Ca2+, and blocks glutamate excitoxicity[31].However, the concentrations required to achieve this effect are nonpharmacologic[32]. Topical administration does not appear to achieve necessary intravitreal neuroprotective concentrations. As such, currently available topical beta-1 adrenergic antagonists should not be used for glaucoma neuroprotection.

Calcium channel blockers

Systemic calcium channel blockers (CCB) cause vasodilation by preventing the intracellular uptake of Ca2+. CCB may improve optic nerve head perfusion, particularly in patients with normal-tension glaucoma[33]. While CCBs have been shown to improve psychophysical testing in a small group of patients, these results have not been confirmed in a large study[34]. Side effects associated with systemic CCBs may limit their practical use. In a small group of patients placed on systemic nifedipine, a significant number were intolerant of the medication and had to discontinue it[35]. A recent prospective population-based study has also shown a positive correlation between systemic CCB use and the development of incident glaucoma. Further prospective studies are needed to determine the safety and efficacy of CCBs. We presently do not make recommendations to glaucoma patients regarding the use of CCBs.

Conclusion

The concept of direct optic nerve protection is in its infancy. Nonetheless research in to inventive delivery –systems improved safety and discovery of additional neuroprotective agents will undoubtedly lead us further in to this promising era in glaucoma therapy.

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