Review Article :

NEUROPROTECTION IN GLAUCOMA MANAGEMENT

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Glaucoma is an optic neuropathy clinically characterized by excavation of the optic nerve head and progressive loss of retinal ganglion cells (RGC). It is still unknown whether optic nerve head changes precipitate RGC death or vice- versa. However, increased intraocular pressure precipitates certain structural and compositional changes changes in the optic nerve head consisting of increased synthesis of several extracellular matrix molecules like Tenasin, Matrix metalloproteinases, NCAM – 180, Collagen 1V and elastin. Some of these events could be due to reactive astrocytes which may be activated by demyelination of adjacent axons, ischemia, mechanical trauma and increased hydrostatic pressure. These reactive astrocytes migrate to nerve bundles and may form large cavernous spaces through the expression of matrix metalloproteinases and may possibly weaken the architecture the lamina cribrosa beams, eventually leading to injury to the RGC axons that pass through these structures. Retinal ganglion cells(RGC) receive inputs from the Bipolar and Amacrine cells and project their axons via the optic nerve to the target areas in the brain, namely the Lateral geniculate nucleus, pretectal nucleus, suprachiasmatic nucleus of the hypothalamus and the superior colliculus. These target areas in turn release signaling factors (including Neurotrophins) that support neuronal survival via retrograde ganglion cell axons. It is the pathophysiology at the optic nerve head which interferes with the transport of signaling factors and also induces an injury signal in the retina. This then results in retinal ganglion cell death by APOPTOSIS which is a complex active cellular process that results in orderly self destruction. Besides this, there is a process of secondary degeneration wherein neuronal damage continues even when the primary cause has been eliminated.

Neuronal death can be conjectured to occur in three stages: axonal injury, death of the injured neuron and injury to and death of the neighbouring intact neurons through secondary degeneration. This concept, described by Kerr et al, has been applied by Yoles and Schwartz to explain progression of glaucomatous damage despite reduction of intraocular pressure and the fact that patients with severe pre-existing damage are more likely to deteriorate despite lower IOPs than those who do not have visual field loss at the time of diagnosis. Besides the neurotrophin factor deprivation, GON maybe a consequence of insufficient blood perfusion to the optic nerve head caused by increased IOP or other vascular risk factors. Glial cell activation may also be an important factor contributing to RGC death in glaucoma. Synthesis of glial fibrillary acidic protein is significantly increased in glaucoma by Astrocytes and Muller's cells. This increased level of retinal glia exacerbates neuronal damage through release of Cytokines, Reactive Oxygen species or Nitric oxide.

Human neural retina contains approximately 1,000,000 retinal ganglions and a significant loss of these neurons from glaucoma can result in permanent visual disability. Therefore to maintain sufficient neuronal function for useful vision one has to (1) prevent death of neurons, (2) Try to maintain the integrity of the dendrites and axons of RGCs or introduce some method of dendritic

sprouting and axonal regeneration, (3) Electrical, biochemical and energetic requirements needed for transmission of impulses that code for colour vision must preserved, (4) The disease process must be arrested.

Neuroprotection is a therapeutic regime that can prevent or delay neuronal cell death and maintain neural function and in many cases of glaucoma where there is progressive structural and functional loss in spite of excellent IOP control, neuroprotection may be the only viable therapy. Amongst the varied agents reported to have neuroprotective activity in the optic nerve are:-

Calcium channel Blockers(CCB): These agents inhibit the entry of Calcium ions into vascular smooth muscle and maybe able to protect the optic nerve head by improving vascular perfusion especially in Normal tension glaucoma(NTG). **Nimodipine** has been found to have significant improvement in both visual field indices and colour vision. However, systemic hypotension prohibits extensive use of the drug. Nocturnal hypotension secondary to antihypertensive medications has been associated with visual field loss in patients with NTG. **Flunarizine**, a potent CCB has been found to enhance RGC survival after optic nerve transaction in mice.

Antiglaucoma medications: **Betoxolol** posseses both calcium channel blocking activity resulting in vasodilatation and also exerts actions on retinal ganglion cells by reversibly blocking glutamate gated currents and subsequent firing of RPG cells. **Brimonidine** has also been demonstrated to neuroprotective action in animal studies by its ability to reduce rate of RGC loss and also to increase endogenous Brain derived neurophin factor.

N-methyl-D-aspartate Antagonists: The NMDA receptor is anion channel that gets activated when glutamate and glycine bind to the receptor complex thus allowing calcium to enter the cell.

Excessive activation of the NMDA signaling cascade leads to

"Excitotoxicity" wherein intracellular calcium overloads neurons and causes cell death by apoptosis. This excessive calcium activates destructive pathways in the mitochondria, stimulates nitric oxide production and certain mitogen activated protein kinases. An NMDA antagonist **Memantine** has shown great promise as an effective agent for the prevention of GON progression. Memantine is a noncompetitive NMDA receptor antagonist derived from Amantidine which blocks the toxic effects of glutamate without significant effects on normal cellular function. **Eliprodil** is another noncompetitive antagonist which provides protection from glutamate mediated cytotoxicity to retinal ganglion cells.

Nitric oxide synthetase inhibitors: Local production of nitric oxide may play a significant role in the development of multiple neurodegenerative diseases. It is produced by the enzyme nitric oxide synthetase the ONH has a role in the pathogenesis of glaucoma. Therefore pharmacological agents that inhibit NOS-2 may have therapeutic value. **Aminoguanidine**, a selective inhibitor of iNOS (inducible nitric oxide synthetase) has been seen to reduce RGC loss by about 70% in a rat ocular hypertension model. A prodrug of an iNOS inhibitor, L-N(6)- (1-iminoethyl) lysine 5-tetrazole amide has also been found to have similar results.

Antioxidants: These agents neutralize other suicide triggers like reactive oxygen species emanating from the glutamate cascade.

Free radical scavengers like Catalase, superoxide dismutase and vitamins C and E mop up loose byproducts during secondary degeneration.

Neurotrophins: These agents increase RGC survival and are capable of being produced by retinal cells. Delivery of this agent by means of

a viral vector has been tried in animal models. Another method of delivering this agent to the eye could be repeated intravitreal injections which may not be well tolerated. Systemic administration will be difficult as these are large protein molecules and cannot readily cross the blood-retinal barrier. Implantation of a sustained release intraocular implant or a transscleral delivery is other modalities of drug delivery but none of these strategies have proved to have any value.

Vaccination: T lymphocytes localize in damaged neural tissue in case of injury. It has been found in animal models that a subset of these T lymphocytes have receptors specific to proteins of the myelin sheath, such as MBP, which have a protective effect on ganglion cell death ,suggesting thereby that a vaccine based on myelin sheath antigens may have therapeutic value in treating optic nerve damage and possibly glaucoma. However, MBP immunization and T cells specific for MBP induce a severe paralytic condition known as EAE thereby preventing its use as a vaccine. A vaccine called COP-1 has shown to reduce ganglion cell death in animal models and therefore this vaccine may play a role in glaucoma therapy as it does not have side effects like MBP immunization.

Ginkgo Biloba extracts: Ginkgo Biloba influences a number of

biological processes including intracellular signaling and neutralizing reactive oxygen species .It is claimed to be effective in a variety of disorders associated with ageing and has also been found to improve both peripheral and cerebral blood flow. Therapy with Ginkgo biloba extracts has shown to improve preexisting visual field defects in normal tension glaucoma in one clinical trial.

Proving clinical efficacy of a neuroprotective agent in a chronic slowly progressive disease like glaucoma is difficult as it may take many years to prove any significant benefit. As of now, antioxidants are being used in many patients with glaucoma but no well defined agent has yet been introduced into the antiglaucoma armamentarium of drugs.

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