

Neuroprotection in Glaucoma

Researchers continue to seek strategies and agents independent of IOP lowering that will protect neurons from apoptosis.

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europrotection refers to mechanisms that protect neurons from apoptosis arising from insult or progressive neurodegenerative diseases. Applicable to Parkinson and Alzheimer diseases and to amyotrophic lateral sclerosis, neuroprotection accelerates biochemical pathways that prevent neuronal injury or blocks others that lead to neuronal death. Only a few neuroprotective treatments have been approved by the FDA.

Although IOP reduction remains the main strategy by which to halt or slow glaucomatous visual damage, this treatment is not effective for all patients. Neuroprotection offers the hope of protecting patients' vision via a different means. More than 500 possible neuroprotective agents have been investigated in the laboratory for the treatment of neurodegenerative diseases, and the FDA approved riluzole and memantine for amyotrophic lateral sclerosis and Alzheimer disease, respectively.

Many promising laboratory results have not translated clinically for glaucoma, but research continues. Currently, there are nine clinical trials on the human trials registry (www.clinicaltrials.gov) for neuroprotection for glaucoma. A few clinical trials have been

completed (eg, memantine, DNB-001, QPI-1007, brimonidine, and oral antioxidants), and others are underway (eg, NT-501, ciliary neurotrophic factor implants for glaucoma, and oral citicoline for radiation optic neuropathy).



POTENTIAL NEUROPROTECTIVE DRUGS AND STRATEGIES IN GLAUCOMA

N-methyl-D-aspartate Receptor Antagonists

Although glutamate is an essential neurotransmitter in the retina, pathologically increased glutamate concentrations produce excitotoxicity,² which can be blocked by N-methyl-D-aspartate receptor antagonists. Memantine is a noncompetitive, low-affinity, open N-methyl-D-aspartate—channel blocker. Relatively well tolerated, this agent has been approved for use in Alzheimer disease, as mentioned, and in vascular dementia. Memantine is an effective neuroprotective agent, as demonstrated in acute animal models of retinal ganglion cell (RGC) death.³ The drug did not prove effective, however, in a prospective, randomized, controlled trial in glaucoma, but the study design and endpoints might have been flawed.⁴

Neurotrophic Factors

Growth factors (neurotrophins) regulate cellular metabolism to maintain a normal cellular milieu. Growth peptides comprise brain-derived neurotrophic factors, nerve growth factors, neurotrophin-3, and neurotrophin-4.^{5,6} Several of these, especially brain-derived neurotrophic factors, promote the survival of RGCs.^{7,8}

Antiapoptotic Agents

Potentially initiated by several events, apoptosis is cell suicide. To reduce apoptosis, either survival pathways can be promoted, or the apoptotic cascades can be inhibited. Experimentally, effector caspase inhibition has been neuroprotective. Calpeptin, a calpain-specific

inhibitor, has been shown in experimental models of glaucoma to provide neuroprotection.¹⁰

Nitric Oxide Synthase Antagonists

Even though Pang et al found no proof for nitric oxide synthase (NOS)-2 release by astrocytes, 11 some experimental models have demonstrated neuroprotection from the inhibition of NOS using 2-aminoguanidine, i-NOS, and L-N(6)-(1-iminoethyl)lysine 5-tetrazole amide. Nipradilol, a $\mbox{\ensuremath{B}}$ - and $\mbox{\ensuremath{\alpha}}$ 1 antagonist, also showed neuroprotective properties. 12,13

Antioxidants

Free radicals produce oxidative stress: these cytotoxic molecules degrade protein in cell components, producing lipid peroxidation, nucleic acid degeneration, and cell death. Antioxidants such as vitamins C and E and enzymatic activity like catalase and superoxide dismutase can decrease the harm. Tea, coffee, wine, dark chocolate, and Ginkgo biloba extract have shown antioxidant properties.

Calcium Channel and Angiotensin Blockers

Calcium inflow accompanies apoptosis. Neuroprotection by inhibiting calcium inflow or by increasing blood flow to the RGCs has been observed with nifedipine and verapamil. As these agents lower blood pressure, however, they also reduce perfusion pressure and may worsen RGC ischemia. 16 Candesartan (angiotensin II type I receptor blocker) provides neuroprotection against RGC loss. 17

Gene Therapy

Expression of the antiapoptotic gene *Bcl-2* and related proteins inhibits cell death. Drug candidates to increase gene expression include the anti-Parkinson agent deprenyl. Flunarizine and aurintricarboxylic acid retard apoptosis after light-induced photoreceptor cell death. ¹⁸

Immunomodulators and Vaccination

An intact peripheral immune system enables RGCs to survive. T cells activate resident microglia and harness blood-borne monocytes, which arrest degeneration and support axonal regrowth. Glatiramer acetate (copolymer-1) may be a neuroprotective vaccine.¹⁹

Geranylgeranylacetone

Heat shock proteins may contribute to RGC death, so geranylgeranylacetone (used for peptic ulcers), which decreases synthesis of HSP70, may be neuroprotective.²⁰

Stem Cell Therapies

Because it is expressed by RGCs, granulocyte-colony stimulating factor is a candidate for neuroprotection. In

addition, oligodendrocyte precursor cells may prevent damage to RGCs.²¹

Bioenergetics

Unexplored in glaucoma models to date, bioenergetics could provide neuroprotection by increasing RGCs' energy supply and improving mitochondrial function. These agents augment the energy-buffering capacity of damaged cells and free radical scavenging while decreasing the abnormal permeability of mitochondrial membranes.²²

Currently Available Topical Medications

Available drugs (α 2-adrenoceptor agonists, β -adrenoceptor antagonists, prostaglandin derivatives, and carbonic anhydrase inhibitors) inhibit neuronal cell death via complex and independent pathways. Specifically, α 2-adrenoceptors inhibit the proapoptotic pathway, α 3 and α 3-blockers inhibit calcium and sodium ion influx into neurons, which follows ischemia and glutamate excitotoxicity. Evidence remains inadequate, however, to prove clinical neuroprotection.

Other Compounds and Alternative Therapies

Erythropoietin was neuroprotective in preclinical models.²⁵ As vasodilators, endocannabinoids are important in neurodegenerative diseases. Many natural compounds (omega-3 fatty acids, carnitine, coenzyme Q10, citicoline, curcumin, danshen, and resveratrol) may confer neuroprotection.²⁶ No large clinical trials, however, support these compounds for glaucoma treatment.

NEUROPROTECTION IN GLAUCOMA: WHERE ARE WE?

Despite the long list of neuroprotective candidates, clinicians lack a proven neuroprotective agent with which to manage glaucoma. Methods to detect changes in RGCs are not sensitive: current endpoints for visual field and optic nerve change are inappropriate for the evaluation of neuroprotective agents' effectiveness.

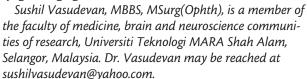
RGC death and its prevention are the subjects of active neurobiological research. Although IOP lowering is still the mainstay of glaucoma treatment, neuroprotection and possibly neuroregeneration may become possibilities in the future. Ultimately, RGC loss must be stopped, and pharmacological neuroprotection for glaucoma is part of the pursuit of effective treatment modalities to improve long-term outcomes.

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