
NEUROPROTECTION IN GLAUCOMA: ROLE OF BRIMONIDINE

New Explanations for Glaucomatous Damage

Four new discoveries have allowed clinicians to better understand glaucomatous damage.

1. Glaucomatous loss shares certain similarities with classic apoptosis.
2. Elevated nitric oxide levels may contribute to ganglion cell loss.
3. Elevated glutamate levels may contribute to ganglion cell loss.
4. There may be an autoimmune component to glaucomatous optic neuropathy.

These findings allow physicians to begin to propose a new approach to the management of this disease – **the concept of neuroprotection**. Although preservation of the optic nerve is the goal of all pressure-lowering therapies, the term neuroprotection in the context of glaucoma has come to mean intervention directed at preserving vision by saving retinal ganglion cells without necessarily lowering the IOP.

Neuroprotection is based on the principle of:

1. Reduce risk factors: lower the IOP, reduce ischemia
2. Promote neuronal survival
3. And/or inhibit cell death

Excess glutamate can be toxic to normal RGC's through over stimulation of N-Methyl-D-Aspartate (NMDA) receptors. The NMDA receptor is a major type of glutamate receptor that when over activated can kill retinal ganglion cell.

The Bcl-2 family of gene proteins performs a central role in regulating apoptosis. Members of Bcl-2 gene family that promote programmed cell death include bad and bax; in contrast, the expression of bcl-2 and bcl-xl suppresses the apoptotic programme. To date, alpha-2 pathways have been identified that increase expression of bFGF, induce bcl-2 and bcl-xl genes, and enhance the availability of important neurotrophic factors.

Brimonidine Tartrate: Role in Neuroprotection

Brimonidine is a α_2 -selective agonist. It is an analogue of clonidine. It is about thirty fold more α_2 selective and has very low affinity for α_1 receptors. Due to this reason, mydriasis and lid lag as found with non-selective agonists like clonidine are eliminated.

Its main mechanism of action is suppression of aqueous formation, but it is also claimed to increase some degree of uveoscleral outflow.

Glaucoma is the second leading cause of blindness worldwide. 66.8 million people world wide suffer from glaucoma and that 6.7 million people have bilateral blindness secondary to glaucoma i.e. vision less than 20/400 or 3/60 in the better eye. The blindness caused by glaucoma is irreversible.

Classic Theories of Glaucomatous Damage

In the normal eye, the retina is a layered array of cells that absorbs light and converts it to an electrical signal. All visual processing in the eye culminates at the innermost retinal layer containing the ganglion cells. Axons from these neurons form the optic nerve and exit the eye at the lamina cribrosa to form their first synapse at the lateral geniculate. Glaucoma damages these axons; this loss is seen clinically as increased cupping or excavation of the optic nerve. If severe enough, glaucoma can lead to visual field compromise and eventual blindness.

The glaucomas generally involve impaired aqueous outflow from the anterior chamber of the eye and a consequently elevated IOP. For all forms of glaucoma, the majority of both medical and surgical therapies are directed at lowering the IOP.

Unfortunately, this is not enough. Even though the IOP can be brought into the normal range, visual field loss and blindness can still develop in 25% to 38% of patients. These observations suggest that factors other than control of the IOP should be considered if glaucomatous blindness is to be prevented. One recent study suggests that 27% of patients would go blind in at least 1 eye after 20 years with glaucoma. Although control of IOP is likely to remain the mainstay of glaucoma therapy, investigation of contributory factors beyond IOP may be helpful if glaucomatous blindness is to be prevented.

Two distinct theories were proposed in 1858 to explain glaucomatous optic nerve damage. Muller suggested that neuronal loss was due to mechanical trauma and that the increased pressure in glaucoma directly compromised the nerve; von Jaeger proposed that vascular compromise was a fault. Almost 150 years later, both theories still have strong proponents, and this debate remains unresolved.

In the late 1960s and early 1970s, the theory was proposed that elevated IOP would block axoplasmic flow at the lamina cribrosa. This might prevent trophic factors from reaching the ganglion cell body and cause the cells to initiate a suicide response resulting in programmed cell death (apoptosis).

Administration of brimonidine 14 hours before injury also resulted in RGC survival that was similar to that when administered immediately after injury.

Thus brimonidine protected the rat optic nerve from secondary damage following mechanical injury to the optic nerve and was nontoxic in an array of experiments designed to evaluate ocular and organ toxicity.

Taken together, the high α_2 -adrenoceptor selectivity, ocular hypotensive efficacy, retinal bioavailability and neuroprotective properties make brimonidine an important addition to the field of anti-glaucoma agent.

Further reading:

1. Surv Ophthalmol 41 (Suppl): S9-S18
2. Drugs and Aging 1998 12 (3): 225-241
3. JAMA 1999 281(4): 306-308
4. Br.J. of Ophthal 1996; 80: 389-93
5. Lancet 1999; 364: 1803-10

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The most significant merit of brimonidine (Brimodin) is its relative systemic safety profile and its postulated function of neuroprotection through upregulation of cellular and neuronal survival factors, such as bFGF1 in response to activation of the α_2 adrenergic receptors, and increase in ocular blood flow.

Animal Study proving Brimonidine as a neuroprotective agent

Role of α_2 -adrenergic receptors in neuroprotection and glaucoma

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Rats were anesthetized and the optic nerve was injured. Brimonidine at 0.1 mg/kg was given by intraperitoneal injection at 14 hours before optic nerve injury or immediately after injury (time 0). Control animals received phosphate buffered saline (PBS) vehicle. Ganglion cell survival was evaluated 12 days later. Neuroprotective effect was the difference between the control and brimonidine group.

Results

Brimonidine at 0.1 mg/kg when injected intraperitoneally, immediately after injury (time 0) resulted in ganglion cell survival of about two-fold.