Treatment of glaucoma continues to be directed at lowering intraocular pressure to decrease the likelihood of disease progression. In the future intraocular pressure reduction might be augmented by other therapeutic approaches. Interest has been increasing in preventing progression of glaucomatous optic neuropathy using approaches based on the premise that glaucoma is a neurodegenerative disease. Neuroprotection of the glaucomatous optic nerve therefore would be an adjunctive therapeutic paradigm for use with conventional intraocular pressure–lowering treatments or by itself.


CURRENT TREATMENT OF GLAUCOMA

Reduction of IOP has been the primary, and often the only, treatment modality for patients with ocular hypertension who are considered to be at risk for developing glaucoma, and for virtually all patients with glaucoma. In clinical practice, reduction of IOP is expected to halt or delay optic nerve damage in these patients. Once initiated, IOP-lowering treatment of both patients with ocular hypertension and glaucoma, usually with eye drops, is generally lifelong unless superseded by surgical intervention. The results of the Ocular Hypertensive Treatment Study, an ongoing randomized trial of medical IOP lowering vs observation, are expected within the next 5 years. Until recently, support for the role of IOP-lowering therapy in patients with glaucoma has derived mainly from uncontrolled or nonrandomized studies. Intraocular pressure–lowering treatment recently has been demonstrated to be beneficial in many, but not all, patients with normal-tension glaucoma. There is a lower rate of progression of visual field loss in patients with normal-tension glaucoma achieving a 30% reduction of IOP by medical or surgical treatment, compared with those in whom it was not lowered.

Seven (12%) of the 61 treated patients reached end points (ie, specifically defined criteria of glaucomatous optic disc progression or visual field loss) compared with 28 (35%) of the 79 untreated control patients, when analyzed on an intention-to-treat basis. That those 7 patients had progressive glaucoma despite a 30% reduction of IOP by medical or surgical treatment is not surprising to many clinicians, particularly those in practice for many years.

Glucoma can worsen despite careful follow-up and good patient compliance with seemingly adequate IOP-
lowering therapy. Medical therapy alone fails to prevent progressive glaucoma damage in many patients. Surgery may succeed more often, but has greater risk associated with its use. In some of these patients with progressive glaucoma, it is possible that IOP has not been sufficiently reduced. In this situation, a lower target IOP range would be more effective. However, it is likely that there are other risk factors, in addition to IOP, that either modify the effects of elevated IOP or independently cause disease progression. Delineation of these risk factors, understanding how they influence optic nerve function and structure, and ameliorating them is necessary to comprehensively treat glaucoma. As the relationship between various risk factors and glaucoma onset or progression is not well understood, and it can be difficult or impossible to ameliorate the risk factors, a more global therapeutic approach may be useful. Neuroprotection, achieved with either current or future drugs, is such an approach and may provide a more encompassing mechanism for treating both nonpressure-dependent risk factors and the effects of elevated pressure (Figure 1).

**WHAT IS NEUROPROTECTION?**

Neuroprotection is a therapeutic paradigm for slowing or preventing death of neurons, in this case retinal ganglion cells and their axons (optic nerve fibers), to maintain their physiological function. Independent of cause, neuroprotection is aimed at blocking primary destructive events or enhancing survival mechanisms of the retinal ganglion cells or optic nerve fibers. In glaucoma, neuroprotection offers a method for preventing the irreversible loss of those cells. An important advantage of the neuroprotective strategy is that it allows treatment of a disease for which the specific etiology is either unknown or differs among patients. This is particularly relevant to glaucoma, a heterogeneous group of disorders that share common characteristic morphological features of the optic nerve head and patterns of visual loss. Theoretically, neuroprotection should be effective independently of whether a particular patient's glaucoma is due to primary or secondary disease mechanisms.

**WHAT DAMAGES THE OPTIC NERVE IN GLAUCOMA?**

Several pathophysiological mechanisms have been hypothesized to have a role in causing retinal ganglion cell death in glaucoma (Figure 2).1,8-10 Retinal ganglion cell viability is hypothesized to be dependent on a balance of positive (survival) and negative (death) stimuli, and they fail to survive if this balance is disturbed (Figure 3).11,12 One specific trigger of retinal ganglion cell death is excitotoxicity.13 Certain excitatory neurotransmitters, such as glutamate, can overexcite a cell via activation of the N-methyl-D-aspartate subclass of receptors. Retinal ganglion cell survival also may depend on certain neuronal growth factors (neurotrophins), such as brain-derived neurotrophic factor and ciliary neurotrophic factor.14 Axonal compression at the lamina cribrosa may cause blockade of retrograde axoplasmic flow from the lateral geniculate nucleus and other retinal ganglion cell targets (eg, superior colliculus, suprachiasmatic nucleus, or pretectal nuclei).15 Death of retinal ganglion cells could thus result from deprivation of these target-derived growth factors.8 Although the actual mechanisms leading to retinal ganglion cell death in glaucoma are still unclear, it would not be surprising if they shared common features with other types of neuronal injury, eg, signaling by reactive oxygen species,11 depolarization of mitochondria,16,17 or induction of transcriptionally regulated cell death.18
Rationale for Neuroprotection

Experimental and pathophysiological studies suggest that the death of retinal ganglion cells in glaucoma occurs by a process of cell suicide or apoptosis.\textsuperscript{19-21} At the present stage of biomedical research, it seems as if dead retinal ganglion cells cannot be replaced. This suggests that protecting a retinal ganglion cell from death is necessary to prevent its irreversible loss of function.

Successful neuroprotection requires that both the functional and structural characteristics of the retinal ganglion cells be preserved to maintain useful vision. Hence, in addition to slowing or preventing death of retinal ganglion cells, the electrical and biochemical requirements needed for function and the integrity of their structural relationships with surrounding cells need to be maintained.

Several approaches to neuroprotection in glaucoma are being evaluated (Figure 3).\textsuperscript{22,23} One possibility is to interrupt the excitotoxic cascade via blockade of the N-methyl-D-aspartate receptors—mediating cell death when retinal ganglion cells are exposed to glutamate.\textsuperscript{24,25} Dreyer et al\textsuperscript{25} have demonstrated elevated levels of glutamate in the vitreous of patients and animals with glaucoma, suggesting a possible causal relationship. Blockade of these receptors may interrupt the effects of axonal injury.\textsuperscript{13,22} Another neuroprotective approach relies on delivering neurotrophins to the retina to compensate for the deprivation of target-derived neurotrophins resulting from blockade of retrograde axoplasmic transport. This might require repeated intravitreal injections in a chronic disease like glaucoma since neurotrophins, which are large molecules, cannot readily cross the blood-retinal barrier. Alternatively, sustained release of a neurotrophin from an intraocular implant might be considered. Another approach to neuroprotection in glaucoma could take advantage of the inherent ability of the retinal ganglion cell to survive after sublethal injury.\textsuperscript{26} Neuroprotective agents that potentiate this survival cascade might maintain cellular function without altering the metabolic and/or proliferative characteristics of uninjured cells.\textsuperscript{27}

Implementation of Neuroprotection

The underlying theoretical basis for a neuroprotective strategy in glaucoma appears sound. Further, considerable data from retinal ganglion cell culture\textsuperscript{22-35} and animal models of optic nerve injury\textsuperscript{25,36-38} support a neuroprotective strategy. No randomized controlled trials have been completed that evaluates patients with glaucoma or any other optic neuropathy. For neuroprotection to become an integral part of our therapy for glaucoma, it is necessary that clinical research complement and extend available basic research.

One development that will surely have an influence on glau-
Conclusions for Neuroprotective Agent

Clinical pharmacological 21 studies in glaucoma have been directed, for the most part, at determining whether a medication adequately reduces IOP with a tolerable side effect profile. Studies to demonstrate efficacy and obtain regulatory approval have been largely short-term and have employed few patients. Unfortunately, there is no simple single parameter to measure neuroprotection. Whether a drug can prevent or delay the progression of glaucomatous optic neuropathy cannot be readily addressed without use of visual function and/or optic nerve structural measures. However, few clinical trials have used visual function or optic nerve structure as an end point for determining treatment effect.

As glaucomatous optic neuropathy is a slowly progressive disease, clinical trials of neuroprotection will necessarily be of much longer duration than is required for determining IOP-lowering effect. In addition, large numbers of patients will be needed. The length of these studies and the large number of patients needed might be reduced by recruiting only those patients who are at higher risk for progressive disease. The use of more sensitive diagnostic techniques for determining visual function and optic nerve structure also may be helpful.

Future Approaches

Although retinal ganglion cells cannot be replaced now, this may change in the future. Recent work suggests that the mammalian CNS has a much greater potential for producing new neurons and repairing damaged regions than previously thought. It may therefore be possible to trace the molecular cascades that lead from a specific stimulus, whether it be mechanical, ischemic, or excitotoxic, to particular alterations in gene expression, and thereby enhance regeneration and/or neurogenesis. Finally, the possibility that stem cell implantation may allow reconstitution of lost retinal ganglion cells could be a powerful method for amelioration of the otherwise irreversible effects of glaucoma on the optic nerve.

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