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treatment of both patients with ocular hypertension and glaucoma, usually with eye drops, is generally lifelong unless superseded by surgical intervention.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.

Glaucoma 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 these 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). 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). One specific trigger of retinal ganglion cell death is excitotoxicity. 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. 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). Death of retinal ganglion cells could thus result from deprivation of these target-derived growth factors. 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, depolarization of mitochondria, or induction of transcriptionally regulated cell death.
Retinal ganglion cells are hypothesized to be dependent on a balance of positive (survival) and negative (death) stimuli. They fail to survive if the balance is disturbed. Enhancing survival stimuli (e.g., neurotrophins) or inhibiting death stimuli (e.g., glutamate) can be neuroprotective. cAMP indicates cyclic adenosine monophosphate.

**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. 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). 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. Dreyer et al 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. 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. Neuroprotective agents that potentiate this survival cascade might maintain cellular function without altering the metabolic and/or proliferative characteristics of uninjured cells.

**Differences Between Neuroprotecting the Brain and the Retinal Ganglion Cell**

Neuroprotection already has been a goal of neurologists and neurosurgeons for several years, as a strategy for dealing with the irreversible effects of central nervous system (CNS) infarction or trauma. Unfortunately, there have been few randomized, double-masked, controlled (phase 3) clinical trials that have shown that any drug can have a significantly beneficial effect compared with no intervention. Therefore, it is reasonable to question why should neuroprotection for glaucoma, a disease affecting the retinal ganglion cell, be effective when it has been unsuccessful in so many other CNS trials so far. This question is of particular concern, as the retinal ganglion cell is itself a CNS neuron, and its axon is insulated and maintained by CNS oligodendrocytes and astrocytes.

One major difference between optic neuropathies (including glaucomatous optic neuropathy) and CNS infarction or trauma is the location of the injury. In optic nerve disease, only the retinal ganglion cell axons may be injured early, and the cell bodies die hours to days later. In most CNS infarctions and trauma, there is immediate injury directly to the cell bodies, and irreversible loss may occur much more quickly. Therefore, the window of opportunity for successful neuroprotection in axonal injuries may be much longer than for cell body injuries. This means that results of trials for neuroprotective agents in CNS diseases in general are not necessarily applicable to glaucomatous optic neuropathies. One of the few successful trials of a neuroprotective agent for CNS injury involved spinal cord injury, which is predominantly a disruption of long myelinated CNS axons.

**Implementation of Neuroprotection**

The underlying theoretical basis for a neuroprotective strategy in glaucoma appears sound. Further, considerable data from retinal ganglion cell culture and animal models of optic nerve injury support a neuroprotective strategy. No randomized controlled trial has 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 glaucoma
Drugs approved to treat glaucoma are used to lower IOP. Whether the use of these drugs also results in preservation of visual function and structural integrity of the optic nerve was not an important consideration in their approval by the Food and Drug Administration. However, it is clear that each IOP-lowering medication has distinct biological activities and, therefore, that their IOP-lowering ability may not correlate fully with their ability to preserve visual function and optic nerve structure. For example, it is possible that 2 drugs that cause equivalent lowering of IOP may lead to different outcomes in retaining visual function. If one of them also can maintain (either directly or indirectly) the health of retinal ganglion cells and their axons, then that drug might be associated with a better visual outcome despite equivalent IOP lowering.

Pharmaceutical companies worldwide have made substantial investments to determine whether their drugs have a salutary effect on visual function and optic nerve structure. The modification of possible risk factors associated with glaucoma progression, such as conditions that lead to ischemia, also have been studied. However, unless these adjunctive measures correlate with enhanced visual function or maintenance of the optic disc and retinal nerve fiber layer, they might not provide justification for a claim for the drug of neuroprotection in glaucoma. The same issues are relevant to the study of drugs that may protect the optic nerve independent of lowering IOP. Regardless of what else it does, a drug should preserve visual function or maintain the structural integrity of the optic nerve if it is to be useful as a neuroprotective agent in glaucoma.

CONSIDERATIONS FOR IDENTIFICATION OF A PUTATIVE NEUROPROTECTIVE AGENT

With our current state of knowledge, candidate neuroprotective drugs should be sought that rescue injured retinal ganglion cells and/or protect healthy retinal ganglion cells. These drugs should be studied in appropriate models. As an example, one might screen drugs by looking at an in vitro model using cultured retinal ganglion cells that have sustained axonal injury. The optic nerve crush model in the rat22 may mimic some, but not all, aspects of glaucoma pathophysiology, and can also be used to screen compounds. More relevantly, candidate drugs can be studied in experimental ocular hypertensive models of glaucoma in the rat37,38 or monkey.39 Human optic neuropathies other than glaucoma (eg, anterior ischemic optic neuropathy or traumatic optic neuropathy) also can be studied as models for rescuing retinal ganglion cells.

As a topically administered drug does not necessarily achieve an appreciable concentration at the retinal ganglion cell or optic disc, whether a topical eye drop can affect retinal ganglion cells, either directly or indirectly, needs to be ascertained. This also is the case for a systemic agent, which would need to be shown to penetrate the blood-retinal barrier.

Finally, it is necessary to ascertain the feasibility of preventing retinal ganglion cell injury and repairing the effects of injury. Prevention is difficult to achieve in glaucoma, as significant damage occurs before detection can be achieved with current methods of visual field testing and optic disc or retinal nerve fiber layer examination. Although the beneficial effect might be limited, repair would appear to be feasible in eyes with known glaucoma.

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.44 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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