# History of Neuroprotection and Rationale as a Therapy for Glaucoma

Leonard A. Levin, MD, PhD; and Patti Peeples, RPh, PhD



Neuroprotection refers to the use of any therapeutic modality that prevents, retards, or reverses neuronal cell death resulting from primary neuronal lesions.[1] It is similar to other cytoprotective therapies (eg, cardioprotection, renoprotection, or vasoprotection) in which the loss of the cell is targeted, not the disease process by which the loss occurs. For example, in cardioprotection, the cardiomyocyte itself is treated rather than the atheromatous plaque within a coronary artery that leads to myocardial infarction. Analogously, in glaucoma, an optic nerve disease, the retinal ganglion cell (RGC) is treated rather than elevated intraocular pressure (IOP) or other etiologies that indirectly cause the death of the RGC. Although IOP lowering and other such therapies can be considered indirectly neuroprotective, by strict definition and by comparison with other cytoprotective therapies, a neuroprotective therapy is directed at the neuron itself.[2]

The road to clinical use of neuroprotectants has been long and uneven. More than 500 products have been investigated for neuroprotective properties in various disease states, including free radical scavengers, antiexcitotoxic agents, apoptosis (programmed cell death) inhibitors, anti-inflammatory agents, neurotrophic factors, metal ion chelators, ion channel modulators, and gene therapy.[3] Agents that are the subject of research range from older established pharmaceuticals to new biotechnology products.

Historically, neuroprotectants have had a low rate of success in the transition from the laboratory to human trials. Despite successful preclinical cell culture and animal model experiments, most of the phase 2 and virtually all of the phase 3 clinical trials of more than 100 neuroprotective drug candidates have failed to demonstrate efficacy, acceptable safety, or patient benefit.[4-6] This has been particularly true in diseases such as stroke[5,7] and head trauma.[8] The commonly posited rationale for these human trial failures is that the animal models do not properly simulate the human disease, or that the variability of the disease in patients is much higher than the variability of the disease in laboratory animals. Another possibility is that the pathophysiology of the disease in humans is intrinsically different from animals. Comparatively, most laboratory animals have smaller and much less developed brains than humans. It is also possible that the ratio of

**Abstract**

Neuroprotection is any therapy that prevents, retards, or reverses apoptosis-associated neuronal cell death resulting from primary neuronal lesions. Although more than 500 products have been investigated for neuroprotective effects, there has been a low rate of success in human trials. Reasons include failure of the animal model to simulate human disease, human disease variability, brain size and development differences, variations in the ratio of axonal to neuronal damage, and lack of efficacy of the compound under study. Other reasons include narrow drug therapeutic index, drug molecular size, the small treatment window after cellular injury, multiple comorbidities of test subjects causing recruitment and statistical challenges, and insufficiently valid and reliable end points. Glaucoma is a neurodegenerative disease for which the neuropathic pathology has been studied since 1972. There have been recent significant advances in understanding the mechanisms for death of retinal neurons, and numerous agents are under development. Memantine, currently approved for Alzheimer's disease and in phase 3 trials for glaucoma progression, is one of the most studied neuroprotectants in glaucoma. Therapies that prevent death of the retinal ganglion cell (neuroprotection), its axon (axoprotection), or both, theoretically should be useful in treating glaucoma.

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axonal damage to neuronal damage differs in human versus animal studies, and this may explain why human neuroprotective studies of stroke have, in general, failed to show efficacy.

Others[4] have suggested that human trials have failed for additional reasons, including the neuroprotectant drugs' narrow therapeutic index (which leads to high levels of side effects), molecular size, and the small window of opportunity after cellular injury. In addition, some of the diseases treated by neuroprotectants are long term and occur in the elderly, who frequently suffer from multiple comorbidities. These confounders pose significant challenges to patient recruitment into clinical trials with typically stringent inclusion and exclusion criteria and present statistical analysis challenges.[4] Moreover, end points for neuroprotectant drug studies in many diseases, including glaucoma, are still being refined, although advances are being made in both objective and subjective clinically relevant outcomes.[2,9,10]

To date, only 2 neuroprotectant drugs have been approved for use by the US Food and Drug Administration (FDA): riluzole, for amyotrophic lateral sclerosis (ALS)[11,12]; and memantine, for moderate-to-severe Alzheimer's disease.[13,14] Neuroprotection trials have also been successful in spinal cord trauma,[15,16] an axonal disease,[17] although this is controversial.[18] Both ALS and Alzheimer's disease are chronic degenerative diseases; thus, the longer window of opportunity for institution of therapy makes the time until therapy is given less critical.[17] Glaucoma has pathophysiologic features of both chronic and axonal neurodegenerative disease; therefore, there is hope that neuroprotection holds promise for glaucoma management.

## Rationale for Glaucoma as a Neurodegenerative Disease

For more than a century, glaucoma treatment has been directed at lowering IOP, yet disease progression continues to occur even in patients with significant IOP reduction, as demonstrated in at least 6 major randomized, controlled, clinical trials.[19-24] It is now understood that glaucoma is an anterior optic nerve disease of which elevated IOP is currently the most important risk factor.[25]

Common neuropathologic features of anterior optic neuropathies are death of RGCs, loss of retinal nerve fiber, nerve fiber bundle visual field defects, and optic atrophy, the last of which helps distinguish glaucoma from other optic neuropathies.[8] However, while the distinctive feature of glaucoma is the change at the optic nerve head,[8] it is the similarities of glaucoma to other optic neuropathies that may lead to newer and better therapies in the future. The RGC is a neuron that sits in the inner layer of the retina and projects a fiber, called an axon, to the brain, primarily the lateral geniculate nucleus in the thalamus. All optic nerve diseases have their irreversible effect on vision because they cause death of RGCs and loss of their axons. Similar to all other neurons, once death of the RGC occurs, it is irreversible because mammalian neurons do not ordinarily replace themselves.

## Neuroprotection Therapy for Glaucoma

Although the possibility of non–IOP-lowering therapy for glaucoma was first recognized in 1972 by Becker et al[26] with the use of diphenylhydantoin for treatment of visual field loss in primary open-angle glaucoma, only recently have significant advances in the understanding of the mechanisms for death of retinal neurons occurred.[2] This has led to the laboratory development of multiple neuroprotective therapies for glaucoma and the clinical study of memantine, a blocker of excitotoxic RGC death, among others.

However, the large number of unsuccessful neuroprotectant drug trials in glaucoma and other disease states is instructive and has demonstrated that animal data and small-sample phase 2 clinical trials in humans are insufficient to make informed clinical decisions regarding the use of these drugs. Well-designed, randomized trials examining glaucoma neuroprotectant agents are in progress. Among the most anticipated are the 2 parallel Memantine in Open-Angle Glaucoma Studies of more than 2000 patients followed for several years. Because memantine does not directly lower IOP, both patients in the memantine groups and the placebo groups were also treated with IOP-lowering therapy. In other words, the effect of memantine combined with IOP lowering was compared with IOP lowering alone. A complete analysis of results has not been published as of January 21, 2008.

In addition to memantine, many other strategies are being considered as neuroprotectants for glauco-

ma, including neuronal growth factors, erythropoietin, reactive oxygen species scavengers, and even vaccine therapies.[27] Possible treatment approaches with these neuroprotectants include their use as monotherapy or as a complement to IOP-reducing approaches, thereby preventing glaucomatous optic neuropathy and blindness.

## Conclusion

Despite the challenging history of neuroprotectants in various disease states, there is a convincing rationale for the use of neuroprotection as a therapy for glaucoma. Glaucoma is a distinctive chronic optic nerve disease in which the primary damage occurs to the RGC axon. The loss of either the RGC or its axon is sufficient to cause visual loss. Therapies that prevent death of the RGC (neuroprotection), its axon (axoprotection), or both, theoretically should be useful in treating glaucoma. This hypothesis is being tested in large-scale clinical trials. There continues to be exciting research within the glaucoma field focused on selecting the most efficacious neuroprotective agents with strong safety profiles, as well as improvements in defining absolute and surrogate end points of neuroprotectant drug studies.

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***Address Correspondence to:*** Leonard A. Levin, MD, PhD, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, Madison, WI 53792-4673. E-mail: lalevin@facstaff.wisc.edu.

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