

Neuroprotection in Glaucoma: Is It Possible?

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Glaucoma is the second leading cause of blindness worldwide, and blindness from glaucoma is irreversible. It is a chronic progressive optic neuropathy associated with characteristic changes in the morphology of the optic disc, pattern of visual field, and death of retinal ganglion cells.

Glaucoma, as we now know, is not a disease of intraocular pressure (IOP). Traditionally, glaucoma was viewed as a disease of elevated IOP, in which visual loss could be prevented by lowering the pressure. Today, glaucoma is viewed as an optic nerve disease in which IOP is currently the most important risk factor available for change. Although lowering IOP has been linked with the prevention of visual loss in many patients, it has not been effective for all patients. Progression of disease despite a significant lowering of IOP has been demonstrated in all of the major, randomized clinical glaucoma trials, including the Advanced Glaucoma Intervention Study (AGIS), the Collaborative Normal Tension Glaucoma Study, the Collaborative Initial Glaucoma Treatment Study Trial, and the Early Manifest Glaucoma Trial.

The primary site of damage in glaucoma appears to be the optic nerve head. It is characterized clinically by thinning of the neural retinal rim and excavation (cupping) of the optic nerve head, which is thought to be caused by axonal injury with subsequent retrograde degeneration of the retinal ganglion cells (RGC). However, as in many neurologic diseases, injury can spread to the connected neurons in the brain by a mechanism called "trans-synaptic degeneration". In trans-synaptic degeneration, target neurons are disconnected from their major afferent pathways, resulting in neural cell shrinkage and death. Trans-synaptic degeneration is a well known process in Alzheimer's disease, amyotrophic lateral sclerosis, brain trauma, and glaucoma. The loss of afferent optic nerve fibers in glaucoma is associated with neuronal changes in target central visual neurons. Ninety percent of optic nerve fibers that arise from retinal ganglion cells terminate in a deep structure of the brain called the lateral geniculate nucleus (LGN). Neurons in the LGN convey visual information to the visual cortex (Fig 1). Therefore, glaucoma is not only a disease of the eye. But it is also a disease of the central nervous system. It was characterized by progressive optic neuropathy, including retinal ganglion cell loss by the so-called programmed cell death, apoptosis¹. Most of the neurons in the central nervous system do not reproduce, and so the loss of retinal ganglion cells cannot be replaced. So, it is important to keep the neurons alive and functional,

because the loss of function is irreversible. The process of keeping these cells alive and functional is called "neuroprotection" and it constitutes a strategy for treating many neurodegenerative diseases and any of the optic neuropathies, including glaucoma.

Weinreb and Levin² defined glaucoma neuroprotection as "a therapeutic paradigm for slowing or preventing the death of RGC and their axons to maintain their physiologic function," and they also stated that "Independent of cause, neuroprotection is aimed at blocking primary destructive events or enhancing survival mechanisms of the RGC or optic nerve fibers." Vision is lost when the ability to transfer information from the eye to the brain is interrupted in diseases of the optic nerve, including glaucoma. At the same time, optic nerve injury results in death of the retinal ganglion cells, the cell which sends fibers (axons) to the brain via the nerve. This death is a type of cell suicide called apoptosis. The specific mechanisms that cause death of RGC are controversial. However, initial damage to the axon followed by secondary events may play a part. Fig 2 shows the sequence of events that lead to RGC death in glaucoma. Initially, a primary injury to the axon occurs, caused by various interdependent processes such as ischemia, mechanical trauma (e.g., elevated IOP), degenerative neuronal disease, and various genetic components. This axonal injury may result in RGC death. The primary phase of damage can lead to changes in the extracellular milieu surrounding the injured neurons and create a toxic environment that initiates an additional, progressive secondary stage of injury in which the

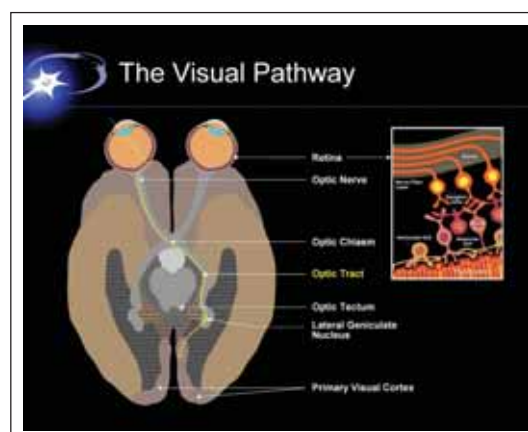


Fig 1. The visual pathway

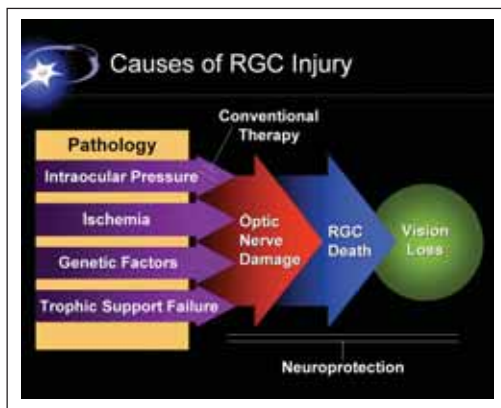


Fig 2. Causes of RGC injury

neighboring neurons are affected—this process is often referred to as the “neighbor-kill effect.” Although the loss of RGC is presumed to be irreversible, the objective of neuroprotective therapy is ideally to prevent neuronal damage associated with the primary insult as well as that which occurs during the progressive secondary stage of injury.

According to Leonard A. Levin, M.D., Ph.D.³, at least three processes may cause axons to die:

- The flow of chemical substances, such as neurotrophins, carried from the brain to the RGC becomes interrupted
- The flow of substances in the reverse direction (from the RGC to the brain) is blocked, leading to accumulation of substances that lead to cell death
- Initial damage to the axon induces a death or similar injury signal to be sent to the RGC body

The mechanisms by which axonal damage signals apoptosis are complex, but if these mechanisms can be interrupted, then RGC death may be blocked. This is called neuroprotection. The viability of RGC is thought to depend on the balance between cell death signals and cell survival signals (Fig 3). A shift in the balance between these signals leads to cell death, and the aim of neuroprotective therapy is to tip the balance in favor of cell survival by either blocking cell death signaling or by enhancing cell survival signaling. Cell death signals include elevated glutamate concentrations, intracellular calcium influx, pro-apoptotic gene expression, generation of nitric oxide and reactive oxygen species (free radicals), and cytokine production. Cell survival signals include growth factors, endogenous antioxidants, and the expression of anti-apoptotic genes. In most cases, the process that ultimately leads to RGC death is a form of “cell suicide” known as apoptosis. Apoptosis is a normal process of genetically programmed cell death that activates various biochemical pathways to destroy cells that are injured or no longer needed. Apoptosis normally serves an important homeostatic function. However, excessive or uncontrolled, apoptosis has been implicated as a fundamental process in the pathogenesis of many diseases including glaucomatous optic neuropathy.

Glutamate is a neurotransmitter that is essential in the communication among neurons. Neurons communicate by using electrical and chemical signals. Electrical signals involve action potentials, whereas chemical signals include neurotransmitters and neuromodulators. Changes in cell



Fig 3. Balancing between apoptosis and cell survival

membrane potentials caused by excessive glutamate levels can result in toxicity. In glaucoma, increased levels of glutamate have been reported at concentrations that are potentially toxic to retinal ganglion cells. Glutamate may reach toxic levels, which will result in too much calcium influx and consequent cell death⁴. Blockage of glutamate receptors may help in the rescue of neuron cell death. Excessive glutamate is one of the excitotoxicity to retinal ganglion cells in glaucoma. Glutamate receptor antagonist that selectively reduces excessive receptor activation without affecting normal function will be clinically tolerated. Memantine, a neuroprotective agent that blocks excessive glutamate receptor activation, but not normal activation, has been recently approved by the Food and Drugs Administration of the US for the treatment of Alzheimer’s disease. Further clinical studies on the efficacy of memantine in the treatment of glaucoma and other neurodegenerative diseases are currently under way.

In conclusion, the neuroprotection strategy in neurodegenerative diseases aims to halt or minimize disease progression by stemming the underlying process of neuronal cell injury and death. The recognition that certain pathogenic processes, such as glutamate excitotoxicity, free radicals, and apoptotic cell death, play a potentially important role in neurodegeneration has led to considerable interest in the use of neuroprotective strategies for the treatment of various diseases including glaucoma. A plethora of data collected from cell culture and animal models of various diseases seem to support a neuroprotective strategy. However, for neuroprotection to become part of the glaucoma therapeutic mainstream, clinical research must complement these extensive basic research achievements. Randomized, controlled clinical trials to evaluate neuroprotection in glaucoma and other diseases have been initiated and are ongoing. Because glaucoma is slowly progressive, these studies require a substantially greater number of patients (thousands vs. hundreds) and more time (years vs. weeks) than is needed to assess the IOP-lowering efficacy of various drugs. It is expected that results from these clinical studies will be available over the next few years.

REFERENCES

1. Weinreb RN. Neuroprotective strategies for glaucoma. *Ocular Surgery News* 2004; 3.
2. Weinreb RN, Levin LA. Is neuroprotection a viable therapy for glaucoma? *Arch Ophthalmol* 1999; 117: 1540-4.
3. Levin LA. Axonal signaling of retinal ganglion cell death. *Ocular Surgery News* 2004; 4.
4. Wheeler LA, Woldemussic E, Lai RK. Alpha-2 agonists and neuronal survival in glaucoma. In: Weinreb RN. *Glaucoma Neuroprotection* 2006: 53-63.