



Graduate Studies

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# Retinal Degeneration and Neuroprotection

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Glaucoma is a disease of the visual system often characterized by higher than normal intraocular pressure (IOP), structural changes within the eye, and a progressive loss of vision. The initial site of injury appears to be the optic nerve head, where retinal ganglion cell axons exit the eye and form the optic nerve. Here, elevated IOP results in shearing and compressive forces that either damage the nerve fibers directly, indirectly by affecting the vasculature that sustains them, or both. The result is a focal point of axon damage that then travels along the optic nerve in both directions, resulting in the retrograde degeneration of ganglion cells within the retina and the anterograde degeneration of their target neurons in the dorsal lateral geniculate nucleus (LGN) of the thalamus.

The research in my laboratory focuses on the cellular changes that occur within the visual system following optic nerve injury. Initial studies combined the use of an isolated retina preparation with intracellular staining techniques (Fig. 1) and confocal microscopy to demonstrate that the earliest signs of retinal degeneration in the glaucomatous eye include structural abnormalities in the ganglion cell's dendritic architecture (Fig. 2).

These studies also documented the concomitant cellular changes occurring within the LGN in glaucoma (Fig. 3).

Since ganglion cells receive all of their synaptic input via their dendrites, our more recent work has combined the isolated retina preparation with intracellular recording and staining procedures in order to focus on the structure-function relations of single ganglion cells in the normal and glaucomatous eye. These studies have shown that although degenerating ganglion cells retain their intrinsic, biophysical, response properties, their spatial-temporal responses to patterned visual stimuli are significantly affected.

A central goal of our ongoing research is the development of neuroprotection strategies aimed at mitigating, or reversing, these structural and functional deficits. Initial studies in cats have shown that brain-derived neurotrophic factor (BDNF), a potent neuroprotectant in the small rat eye, also is an effective neuroprotectant in primate-sized eyes following optic nerve injury (Fig. 4). Additional studies have shown that treatment of the eye with BDNF not only enhances the number of ganglion cells that survive the optic nerve injury, but that these neurons also retain their normal dendritic structure. More recent studies are aimed at determining the extent to which these surviving neurons retain their normal visual response properties. These studies employ non-invasive testing of visual integrity using electroretinographic (ERG) analysis, as well as intracellular measurements. Since it is well-known that neurons depend on interactions with their target neurons for survival, additional work is aimed at evaluating whether an enhanced level of neuroprotection can be achieved by providing BDNF not only to the eye alone, but also to its primary target, the LGN, where we have found BDNF also is a potent neuroprotectant.

**Figure 1:** Intracellular injection of a single ganglion cell with the fluorescent dye Lucifer Yellow CH.

**Figure 2:** Confocal microscope reconstructions of ganglion cells from a normal (left) and glaucomatous (right) eye. Note the significant decrease in dendritic branching and distal process thickness in the glaucomatous cell.

**Figure 3:** Frontal sections through the LGN of a normal (left) and glaucoma-affected (right) LGN. While the normal LGN shows uniform staining across its eye-specific input layers, the glaucomatous LGN has a striped appearance, owing to the small, pale-staining, degenerated neurons located within those layers receiving retinal input from the glaucomatous eye.

**Figure 4:** Dose-response histogram showing the neuroprotective effects of BDNF in the eye following optic nerve injury.

