

Koniocellular Pathway Damage in Glaucoma

Ocular hypertension affects the blue/yellow neurons.

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In glaucoma, the death of retinal ganglion cells causes vision loss.¹ Glaucomatous damage implicates retinal ganglion cells in the major vision pathways conveying motion and red/green color information—the magnocellular and parvocellular pathways, respectively. Numerous studies have demonstrated that the damage to these pathways extends from the eye to the lateral geniculate nucleus, which is the major relay station between the eye and the visual cortex. Newer evidence points to the additional involvement of a more recently characterized “third channel” in glaucoma called the *koniocellular pathway*.^{2,3}

MAGNOCELLULAR, PARVOCELLULAR, AND KONIOCELLULAR NEURONS IN THE LATERAL GENICULATE NUCLEUS

Ninety percent of retinal ganglion cells project to the lateral geniculate nucleus in the brain. Here, the targets of these retinal ganglion cell populations are exquisitely segregated anatomically. When examining a cross-section of the lateral geniculate nucleus, magnocellular and parvocellular layers are easily identified with the Nissl stain in which the neuron cell bodies show a dark blue laminar pattern and six-layered organization (Figure 1A). Magnocellular neurons are located in the most ventral layers (1 and 2), whereas parvocellular neurons are found in the remaining four dorsal layers (3 through 6). Koniocellular neurons cannot be identified using the Nissl stain, but they can be localized using a cell-specific marker as seen in the control (Figure 1B).

RETINAL GANGLION CELLS AND BLUE/YELLOW FUNCTION

It is well established that distinct populations of retinal ganglion cells respond selectively to specific visual stimuli.² In the primate visual system, retinal ganglion cells projecting to magnocellular, parvocellular, and koniocellular layers respond preferentially to motion, red/green color, and blue/yellow stimuli, respectively.² Despite some morpho-

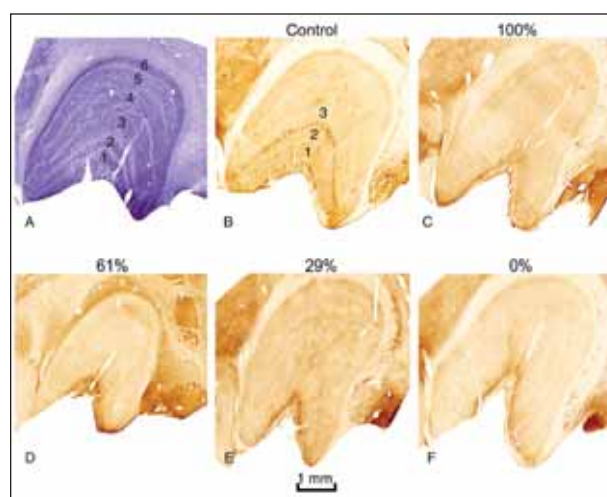


Figure 1. In the lateral geniculate nucleus section of a control monkey stained with Nissl, the majority of neurons are arranged in six layers, indicated by numbers (A). Immunostaining for CaMKII-alpha of the control lateral geniculate nucleus shows CaMKII-alpha neurons between layers 1 and 2, between layers 2 and 3, and below layer 1 (layer S) as well as additional, sparsely distributed neurons between and within the remaining layers (B). Experimental, left lateral geniculate nuclei connected to the ocular hypertensive right eye in an experimental monkey model of glaucoma with varying degrees of retinal ganglion cell axon loss are immunostained for CaMKII-alpha (C through F). These nuclei show virtually no CaMKII-alpha neurons between layers 1, 2, and 3 for all eyes with chronic IOP elevation and retinal ganglion cell axon loss of 100% (C), 61% (D), 29% (E), and zero (F). Layer S CaMKII-alpha neurons appear to be unaffected (B through F). Scale bar indicates 1 mm. (Reprinted with permission from Yücel YH, Zhang Q, Weinreb RN, et al. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. *Prog Retin Eye Res*. 2003;22:465-481.)

logic variation, different cell types are not clearly distinguishable in the retina or optic nerve by histological methods and are even less distinguishable in pathologic states such as glaucomatous neural degeneration.

In glaucoma, psychophysical visual perimetry tests detect vision loss caused by retinal ganglion cell death.¹ Recent studies using short-wavelength automated perimetry showed that blue/yellow function is altered during the early stages of glaucoma and that this test can therefore diagnose glaucoma earlier than standard automated perimetry.⁴⁻⁶ Little is known of the anatomic and pathologic correlates of the blue/yellow visual deficits in glaucoma, however.

MAGNOCELLULAR AND PARVOCELLULAR NEURON DAMAGE IN GLAUCOMA

Most of our knowledge of brain changes in glaucoma derives from studies performed in the experimental monkey model of glaucoma. Central visual pathways in nonhuman primates are similar to those in humans,² and glaucomatous damage in the experimental monkey model mimics that found in human glaucoma.⁷ Accumulating evidence shows that the magnocellular and parvocellular pathways in the lateral geniculate nucleus are damaged in glaucoma. Altered expressions of a cytoskeletal protein called *neurofilament* and of a presynaptic molecule called *synaptophysin* are observable in both magnocellular and parvocellular neurons in the glaucomatous lateral geniculate nucleus.⁸ A relative reduction in metabolic activity detected with the mitochondrial enzyme cytochrome oxidase is also evident in both magnocellular and parvocellular neurons in the lateral geniculate nucleus.^{8,9}

Neuropathologic changes consist of neuron shrinkage and loss.¹⁰⁻¹³ The shrinkage of lateral geniculate nucleus neurons occurs relatively early in glaucoma and prior to detectable optic nerve fiber loss.¹² Evidence of cell death in the glaucomatous lateral geniculate nucleus has also been reported.^{10,11} The shrinkage and loss of magnocellular and parvocellular relay neurons in the lateral geniculate nucleus increases with escalating injury to retinal ganglion cell axons.¹² Relay neurons are those specifically destined for the primary visual cortex, and studies of the visual cortex confirm changes at this level as well.¹³⁻¹⁵ Further studies are needed to determine the earliest changes in the magnocellular and parvocellular layers.

KONIOCELLULAR NEURON DAMAGE IN GLAUCOMA

Koniocellular neurons comprise the third channel in the primate. They are located between and within the principal layers of the lateral geniculate nucleus. These neurons receive their retinal input from blue/yellow retinal ganglion

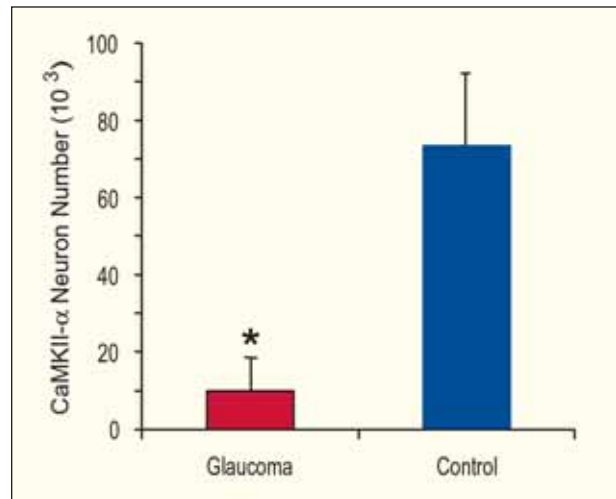


Figure 2. The mean numbers of CaMKII- α neurons in the lateral geniculate nuclei of the control ($n=5$) and glaucoma ($n=7$) groups are shown as a blue and red bar, respectively. Error bars indicate standard deviations. The mean number of CaMKII- α immunoreactive neurons was significantly reduced in ocular hypertensive monkeys with and without significant glaucomatous damage. The asterisk indicates $P<.05$. (Reprinted with permission from Yücel YH, Zhang Q, Weinreb RN, et al. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. *Prog Retin Eye Res*. 2003;22:465-481.)

cells, and they project into cytochrome oxidase-rich blobs in the visual cortex that are involved in processing blue/yellow chromatic information.^{2,3,16} Although not readily identifiable in Nissl-stained sections (Figure 1A), it is known that the koniocellular neurons in the lateral geniculate nucleus can be readily and selectively identified with the cell-specific marker called *calcium/calmodulin-dependent kinase type II- α* (CaMKII- α isoform), which identifies a major postsynaptic density protein.¹⁷

In normal monkeys, lateral geniculate nucleus sections immunostained for CaMKII- α show a large population of these koniocellular neurons in layer S ventral to layer 1, between layers 1 and 2, and between layers 2 and 3 (Figure 1B). Sparsely distributed CaMKII- α neurons have been observed between and within the remaining principal layers.^{2,3} In all monkeys with chronically elevated IOP, this CaMKII- α immunoreactivity was dramatically reduced (Figure 1C through F) compared with controls (Figure 1B). Surprisingly, a strong decrease was also seen in monkeys with minimal-to-no retinal ganglion cell axon loss (Figure 1D through F). It therefore appears that the loss of the postsynaptic density protein of the koniocellular neurons occurs even with elevated IOP but without

detectable retinal ganglion cell loss. This finding suggests an early alteration in at least the function of these neurons in response to elevated IOP.

The number of CaMKII- α neurons was assessed using three-dimensional stereological methodology as previously described.¹⁰ The number of these neurons located within and between the principal layers of the lateral geniculate nucleus was significantly lower in the glaucoma group compared with controls (Figure 2). Similarly, the number of CaMKII- α neurons was significantly decreased for all monkeys with experimental glaucoma, including those with minimal-to-no retinal ganglion cell axon loss, compared to the lower 95% confidence limit of the control group. This finding suggests that damage to the koniocellular pathway is evident in all animals with chronic ocular hypertension and no significant optic nerve fiber loss, and that this damage involves a molecule critical to synaptic strength.

IMPLICATIONS

We have previously discussed the implications of neural degeneration in the magnocellular and parvocellular pathways in experimental glaucoma as they relate to motion and red/green visual deficits in the disease process.¹² Although it is not yet known what mechanisms are involved or whether apoptosis is the dominant mechanism, oxidative damage seemingly is implicated.¹⁸ Neurochemical changes in koniocellular neurons in the presence of ocular hypertension, without significant retinal ganglion cell axon loss, suggest that elevated IOP may alter the blue/yellow koniocellular pathway in the central nervous system in early glaucoma. This finding is consistent with the observation that short-wavelength automated perimetry (which uses a blue stimulus on a yellow background) detects glaucoma earlier than standard perimetry in long-term studies.⁴⁻⁶ In glaucoma, damage to target neurons in the lateral geniculate nucleus apparently occurs not only in the magnocellular and parvocellular pathways but also in a third channel, the koniocellular pathway responsible for blue/yellow processing.

Blue/yellow deficits are an early change in glaucoma patients. The evidence of damage to the koniocellular pathway may well be the pathologic correlate of this early visual-modality deficit. Further studies assessing pathologic correlates in the central visual system are needed to understand the pattern and the modalities of visual loss in patients with glaucoma.¹⁹ □

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