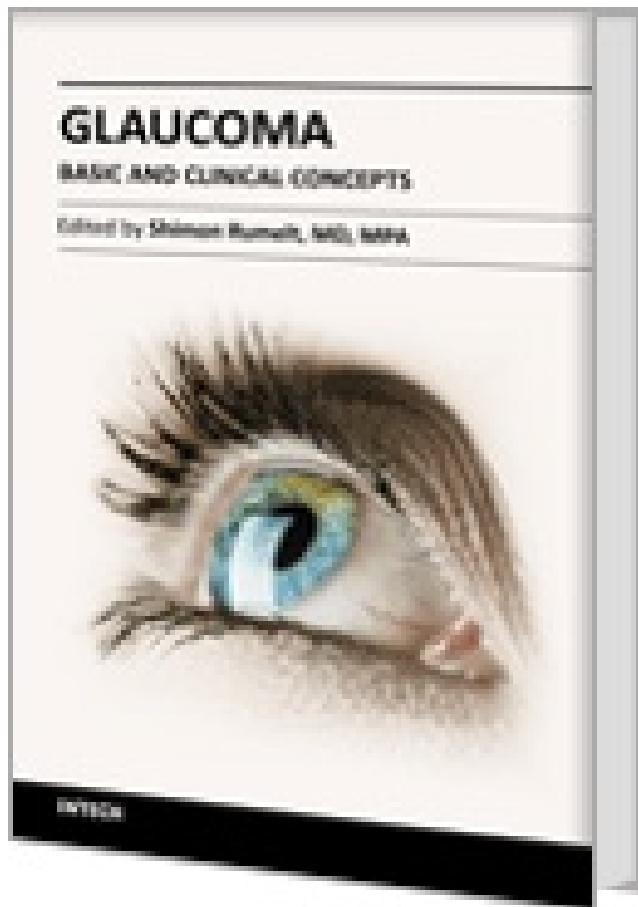


GLAUCOMA - BASIC AND CLINICAL CONCEPTS

Edited by **Shimon Rumelt**



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Adaptive Changes in the Retina and Central Visual Areas in Glaucoma

Sansar C. Sharma¹, Jin Li² and Elena Vecino³

¹*Department of Ophthalmology, Cell Biology and Anatomy,
New York Medical College, Valhalla, NY 10595*

²*Department of Neurology, New York Medical College, Valhalla, NY 10595*

³*Faculty of Medicine, Univ. del País Vasco, Leioa,*

^{1,2}*USA*

³*Spain*

1. Introduction

Glaucoma with or without elevated intraocular pressure (IOP) leads to the loss of retinal ganglion cells and the visual fields loss. Most studies of glaucomatous conditions have dealt with the pathophysiology within the retina. In many cases, retinal ganglion cell death continues after medical or surgical management of elevated IOP. Relatively little attention has been given to the functional consequences of the remaining retinal ganglion cells following normalized intraocular pressure. Here we review the studies dealing with loss of visual acuities and contrast sensitivities of the glaucomatous retina with changes that follow the dendritic arbors of remaining ganglion cells and compare with the adaptive changes observed in the terminal areas of the optic axons in the brain visual centers.

2. Background

Glaucoma is the most common neurodegenerative disease of the eyes, leading to the blindness. The loss of vision in glaucoma has been attributed to the retinal ganglionic cell death (RGCs) and optic nerve axonal loss. In a recent study, advanced glaucoma intervention study, the relationship between intraocular pressure control and the visual field deficits has been established (1). This report has established the role of elevated IOP, in clinical trials, to the initiation of glaucoma and further elaborated that reduction of IOP can reduce the progressive vision loss in glaucomatous patients.

In the pathology of the glaucoma, visual field losses first occur in the peripheral retina and progressively lead to the loss of all vision and complete blindness. The main therapy for the treatment of glaucoma has been the reduction of IOP that stabilizes the vision loss. However, in certain population, the visual loss continues in spite of the reduction of IOP.

The death of RGCs in glaucoma is primarily apoptotic in experimental animals (2, 3) and in Human (4). The exact mechanism, which initiates the cascade of death signals in RGC of glaucomatous eye, is unclear. Similarly, how the elevation of IOP translates or triggers changes in either RGC or its effect to the optic disc and/or the optic axons is uncertain. Actually over the past 20 years, more efforts have been made in searching for the perfect

model that replicate human disease yet nothing close to human disease process has emerged in experimental animal models. However, these efforts have led to myriad theories of the initiation of changes in the prelaminar optic axons supporting the assumptions that optic axons are injured first followed by the death of RGCs. Similarly data exist that leads one to believe that RGCs are directly affected by elevated IOP.

Relatively less efforts has been made in deciphering how the pressure triggers changes in cells other than RGCs. In animal models of glaucoma, activation of microglia leads to proliferation and hypertrophy, visible within hours after the initial insult (5). The mechanisms of activation, proliferation, and hypertrophy are not understood. In glaucomatous eye, either the optic nerve or the retina initiates changes in microglia that have been known to trigger the formation of reactive oxygen species. The reactive oxygen species activate nuclear factor kappa B (NFκB), which then results in the expression of proinflammatory cytokines. Persistence of these factors leads to the peroxidation of lipid and the activation of apoptotic neuronal death pathways. Speculations regarding such a role for microglia in glaucoma have been made, although no definite answers have yet emerged.

Similarly, other glial cells, such as astrocytes, become hypertrophied and have enlarged end feet at the retinal blood vessels in glaucoma.

It has also been reported that astrocyte migration occurs in response to neuronal injury through the action of myriad growth factors, such as epidermal growth factor (6); cytokines, such as tumor necrosis factor (TNF- α) and interleukin 1 alpha (IL-1 α) (7); and other mediators, such as adenosine triphosphate (ATP) (8). This migration is considered an important component in the remodeling of the optic nerve head in glaucoma (9). Reactive astrocytes migrate from the cribriform plates into the nerve bundles and synthesize neurotoxic mediators such as nitric oxide (NO) and TNF- α , which may be released near the axons causing neuronal damage (10, 11). Agents that inhibit the migration of astrocytes by transforming growth factor B (TGF β) and myosin light chain kinase pathways were suggested for glaucoma treatment (12).

Müller cells have also been shown to respond to growth factors and cytokines (13), though their role in initiating RGC death in glaucoma is unclear.

Recent evidence suggests that metabolic stress to astrocytes releases ATP which leads to the propagation of calcium waves causing axonal loss (14). Reactive microglia then follows the gradient of ATP to remove the axonal debris. The marked activation of microglia in the retina, optic nerve, and tract was postulated to accompany ongoing axonal degeneration. The degree of activation in the optic nerve correlated with axonal damage (14). Interestingly, as microglia is the major cell population in the central nervous system with the potential to act as antigen-presenting cell, upregulated major histocompatibility complex (MHC) antigens were not sufficient to stimulate significant T-cell infiltration in a mouse model of glaucoma (15,16).

The steps of programmed cell death in glaucoma are similar to the steps in other neurodegenerative diseases, such as Alzheimer disease (AD), Parkinson disease, or even Huntington diseases. The agents that cause these diseases may be varied. There are certain common features, for example, the death of RGCs in glaucoma. In a recent article Crish et al. (16) showed that distal axonal injury appears early in mouse glaucoma, similar to the distal changes in AD and other neurodegenerative diseases. These authors showed the changes in axonal transports progress from the distal to the proximal end. The early changes showing the breakdown of optic axonal terminals were seen in superior colliculus followed by changes in the optic axons and finally in the retina. They further elaborated that in addition

to the failure or decrease in axonal transport (distal to the proximal area) the axonal terminal persisted in the colliculus. There is absolutely no information regarding this topic in Human glaucoma.

Glaucomatous loss of RGC can cause neurodegeneration in the central visual pathways in animal (17) and in humans (18). Recent advance of functional magnetic resonance imaging (fMRI) provide functional assessment of visual changes in glaucoma patients, which correlated, well with the loss of visual field in the eye (19). Extensive reorganization of visual terminal area was detected in macular degeneration patients (20). In rat glaucoma model, the visual scotoma was not apparent in the tectum two to three weeks after surgery, and larger receptive fields on the periphery represent early signs of altered geometry of the retinal projections (21). It was further assumed that following the death of larger cells on the periphery, the remaining ganglion cells expanded their axonal arbors in the tectum leading to the enlarged receptive fields. The size of the receptive field correlated with the duration and magnitude of intraocular pressure elevation. In primates glaucoma RGC death leads to changes in the lateral geniculate nucleus (LGN) and visual area 1 where cell loss and the shrinkage of lateral geniculate nucleus was noted (23). Similar changes have been shown in the death of specific cell types in the LGN (22,24,28).

In spite of massive literature that has emerged in the past decade regarding glaucoma, we are still uncertain regarding the initiation of RGC death. Relatively little attention has been given regarding the remaining RGC's function following medical or surgical intervention to reduce the IOP and subsequent RGC death. In addition to observed scotoma, do remaining RGCs after glaucoma IOP management adapt to or show changes in their connectivity patterns to the terminal center of the optic axons in the brain?

There are ample scientific evidences suggesting that retinal photoreceptor degeneration can lead to remodeling of the retinal circuitry (for a recent review see Ref. 25). It has been reported that even adult retina shows signs of neuronal plasticity as evidenced by the presence of hypertrophy and axonal sprouting in bipolar, amacrine and photoreceptors.

In monkey retina with elevated IOP, retinal ganglion cells showed shrinkage of dendritic arbors (17). During non-human primate development, plasticity of RGC dendritic arbors and axonal terminals has been observed (25); however, there is a paucity of data supporting such claims in the adult retina. In monkey glaucomatous retina, there was no increase in RGC soma size or dendritic arborization (26); however, a decrease in the dendritic field sizes of the RGC was reported within 3-6 months of induced glaucoma. In monkeys, Smith et al. (27) reported visual deficits in long-term glaucoma as a consequence of RGC loss with no changes in the functional property of the surviving neurons. In addition, loss of some lateral geniculate neurons and reduction in the soma sizes of others were observed.

2.1 Evaluation of recent findings

In experimental rat glaucoma, ganglion, amacrine, and rod bipolar cell loss was observed within 5 weeks of elevated intraocular pressure (IOP), suggesting that inner nuclear layer cells of the retina were affected as well (36,37). We previously showed 3-4% RGC death per week in glaucomatous rats (29). The IOP elevation was induced by episcleral venous cauderyzation. In these animals, IOP usually returned to normal after 10-12 weeks of elevation, possibly due to revascularization. During the period of elevated IOP in the experimental eyes, the remaining ganglion cell soma increased in size of all RGC types. This increase in soma size can be attributed as a precursor to their death. Another possibility is derived from developmental studies on the retina that points to the fact that increase in

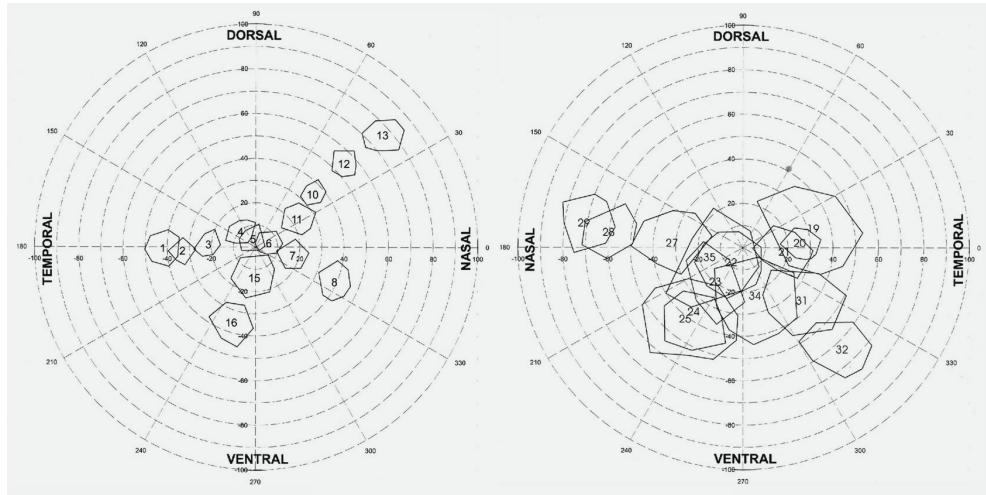


Fig. 1. The retinotopic projective maps in a normal rat when recorded from the electrode positions place on the contralateral superior colliculus. Figure on the left shows numbers 1-16 are representative examples of the visually driven receptive field sizes form the tectum when driven by a normal eye. Receptive field sizes were between 12-25° degrees. The right visual field map shows visually driven receptive field sizes (positions 19-35) in glaucomatous eye that are almost doubled in size when compared to normal. In these topographic mapping there was no overlap of receptive fields in the normal eye mapping, however, experimental glaucomatous eye showed numerous overlapping receptive fields. The normal order of the map was degraded. Many other abnormalities were seen in other maps

soma size of RGC is linked to the soma density. As in glaucomatous RGC, when the cell number decreases, the remaining ganglion cells may hypertrophy. Upon the induction of elevated IOP in pigs using episcleral venous occlusion as in rats (32), Ruitz-Ederra et al. similarly showed an increase in the mean soma area of the remaining RGC (31). A recent study in rat glaucoma showed the neuroprotective effect on retinal ganglion cell survival following systemically administration of bromodimidine and it further prevented the increase in soma sizes usually associated with RGC death (38). Additionally, because RGCs are ensheathed by Müller cell processes, these processes must change their milieus to allow the soma to increase in size. These findings stand in contrast to findings in the glaucomatous monkey retina, where all retinal ganglion cells shrink in size, perhaps due to the constraints of very tight Müller cell processes that may not allow expansion (30). Future studies must explore the possibility of ganglion cell dendritic arbor expansion following the breakdown of Müller cell ensheathment.

In addition to soma size increases in rat RGCs, Ahmed et al. also showed the increase in the dendritic arbors of the remaining ganglion cells in glaucomatous eyes (28). Do these changes observed in remaining RGCs have compensatory effects on the target centers as well? Towards this goal visually evoked receptive fields were mapped onto the superior colliculus contralateral to the experimental glaucomatous eyes (21).

Recent evidence from mouse and rat studies showed that the optic axonal terminal synapses degenerate from the distal to proximal direction and precede the degeneration and death of

RGCs (33-35). We theorize that the larger visual receptive fields in the superior colliculus of rats with elevated IOP may be the consequence of expanding terminals of the intact axons into spaces vacated by dying retinal axon terminals (22). Within 6-8 weeks of induced glaucoma, electrophysiological mapping showed no significant changes in receptive field sizes when recorded in the superior colliculus. Dramatic changes were not observed until 4-10 months following IOP elevation (22).

Visual receptive fields measured in the contralateral superior colliculus fall in the range of 15 to 20° (Figure 1A) in normal animals. Receptive fields measured 4 months later in experimental animals with elevated IOP were in the range of 40 to 60° (Figure 1B). These observations indicate some adaptive changes.

2.2 Changes in axonal terminal arbors

Anatomical evidences for observed enlargement of receptive fields in experimental glaucoma point to the increase in the axonal terminal arbors of the remaining retinal ganglion cells axons in the contralateral superior colliculus. Figure 2 shows the morphology of RGC axonal terminal in the superior colliculus. The axons at proximal and distal portion of superior colliculus (Figure 2A and 2C) in the normal IOP animal are displayed. With elevation of IOP for 4 months, the axons at the same level were enlarged and more terminal branches were identified (Figure 2B and 2D). This suggests that surviving axons may occupy the territory of the dead axons.

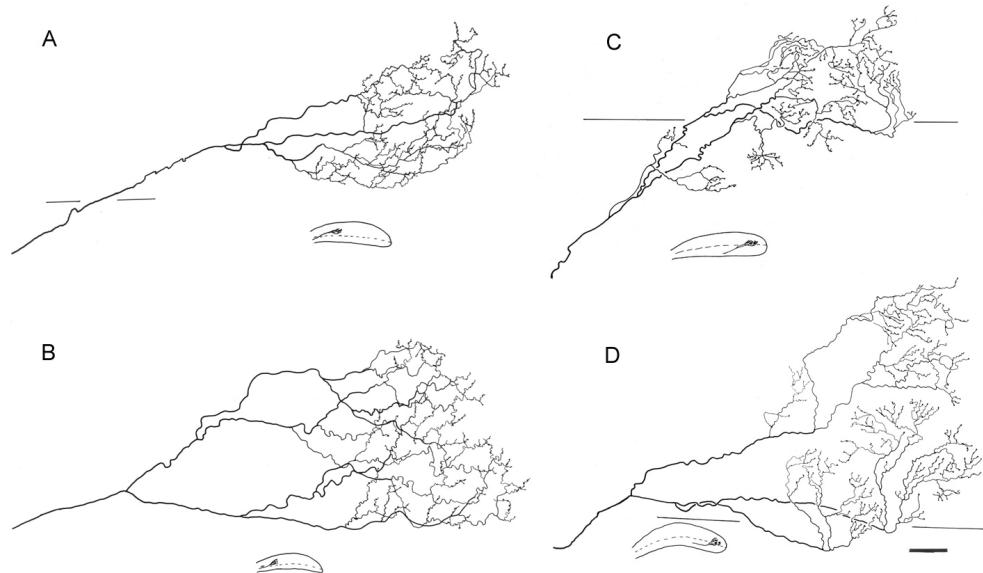


Fig. 2. Camera lucida drawing of the axonal arbor in the mid rostral (Fig. 2A) tectal region of a normal rat, total area of the terminal was $11250 \mu\text{m}^2$. In the glaucomatous animal, the area of terminal axonal arbor at similar location to the normal was $12480 \mu\text{m}^2$ (Fig. 2B). In the caudal tectum of normal rat, the area of the normal optic axonal terminal was $14290 \mu\text{m}^2$ (Fig. 2C) whereas it was $18060 \mu\text{m}^2$ in glaucomatous side (Fig. 2D). It was also noted that these were less vericosities and relatively less dense boutons when compared to the normal

The functional consequences of the changes observed in glaucomatous animals following changes in RGC somas and dendritic arbors of the remaining ganglion cells and the axonal terminal arbors in the contralateral superior colliculus, as described above, were determined psychophysically in the experimental animals. Slow horizontal head and body rotation occurs in rats when the visual fields are rotated around them. These optomotor responses can be readily reproduced. When one eye is closed, only motion in the temporal to nasal direction for the contralateral eye evokes the tracking response. In these animals, visual acuity refers to the maximal spatial frequency capable of evoking an optomotor response. In a normal animal, the visual acuity of the right and left eyes is identical in monocular or binocular viewing conditions. In an experimental eye of elevated IOP, the visual acuity was significantly lower when compared to the control eye ($p < 0.0005$). In addition, the contrast sensitivity as a function of spatial frequency was also studied. At all spatial frequencies studied, the contrast sensitivity of the experimental eye was lower than the control eye ($p < 0.0005$) (39).

2.3 Future directions

The contrasting changes seen in studies involving rat and those involving human glaucoma are at first unsettling. We strongly believe that the following studies need to be undertaken in human.

- a. Longitudinal studies using optical coherence tomography (OCT) with adaptive optics to discern changes in different retinal cell types during the progression of glaucoma.
- b. Studies of the progression or regression of scotomas in human patients following management of elevated IOP either surgically and/or medically

If there are documented changes, one can pursue the means to induce adaptive changes. At present one can only partially block the progression of glaucomatous scotoma and one assumes that partial vision is better than no vision. We must therefore seek the new avenues to overcome our limitations.

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