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MECHANISM FOR CELL DEATH IN GLAUCOMA**

by

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# INTRACELLULAR FLOW IN OPTIC NERVE AXONS: A MECHANISM FOR CELL DEATH IN GLAUCOMA

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**Abstract:** Glaucoma is characterised by elevated intraocular pressure and a progressive loss of retinal ganglion cells, resulting in optic neuropathy. Although it is evident that the raised intraocular pressure somehow affects the retinal ganglion cells, the exact mechanism of glaucomatous neuropathy remains unclear. We propose a potential mechanism for the death of retinal ganglion cells, whereby elevated intraocular pressure causes fluid to permeate the axonal membranes, creating a passive intracellular fluid flow within the axons of the retinal ganglion cells. We hypothesise that this flow locally depletes the concentration of adenosine triphosphate (ATP) within the axons, disrupting axonal transport and leading to cell death.

**Keywords:** *glaucoma, intraocular pressure, optic nerve head, intracellular flow, mathematical model.*

## 1 Biological outline

Glaucoma is a disorder characterised by elevated intraocular pressure and a progressive loss of retinal ganglion cells. Although it is the second most common cause of blindness in Western countries, aspects of glaucoma remain poorly understood. Most notably, the mechanism by which raised intraocular pressure affects the retinal ganglion cells is still enigmatic. A number of different theories have been put forward, but these proposed mechanisms are unable to explain the observation of Balaratnasingam et al. (2007) and others that elevated intraocular pressure leads to a major interruption of active axonal transport (AAT) near the optic nerve head.

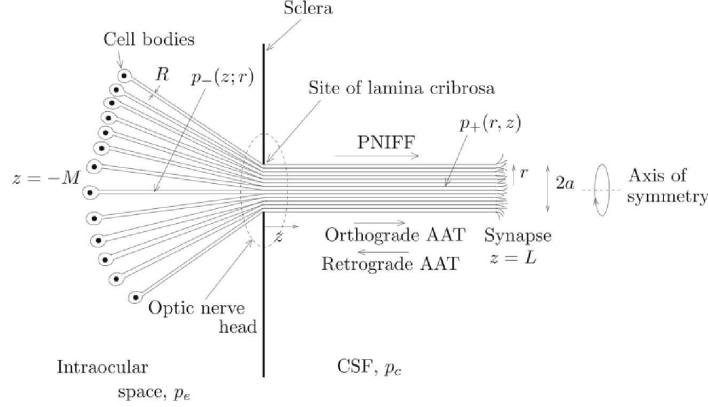
AAT is the process whereby vesicles containing biomolecules are transported along microtubules from cell body to synapse or from synapse to cell body. This process is essential to cell survival and it depends on there being a supply of adenosine triphosphate (ATP) throughout the axon. Thus, a mechanism by which elevated intraocular pressure leads to a depletion of ATP near the optic nerve head would explain the localised failure of AAT and consequent cell death observed in glaucoma.

We have developed a mathematical model of a potential mechanism for glaucoma in which the pressure difference between the intraocular space and the cerebrospinal fluid sets up a passive flow within the axons of the retinal ganglion cells (Band et al., 2009). If this passive neuronal intracellular fluid flux (PNIFF) is sufficiently fast, advection of ATP will dominate over diffusion, leading to a localised depletion of ATP in the fast-flowing regions. We find that the modelled flow is most severe near the optic nerve head, especially towards the periphery of the optic nerve. This model prediction agrees with the observation that glaucoma progresses by affecting peripheral vision before it affects central vision.

## 2 Mathematical model

The geometry of our model is depicted in Figure 1. In the optic nerve, a cylindrical coordinate system  $(r, z)$  is used, where  $z$  measures the distance from the lamina cribrosa along the axis of the nerve and  $r$  represents the radial position of an axon within the nerve of total radius  $a$ . In the eye, the axons are dispersed throughout the retina and so we let  $z$  represent the distance along an individual axon and use  $r$  to distinguish axons according to their radial position in the nerve. The large number of axons in the optic nerve (about  $10^6$ ) enables us to treat this as a continuum problem. Thus, the intracellular pressures in the eye region and the nerve region, taken to be  $p_-(z; r)$  and  $p_+(r, z)$  respectively, can be treated as smoothly varying continuous functions of  $r$  and  $z$ .

The axon walls are permeable to water and we assume that the transmural flux is driven only by the transmural pressure difference. Equating the change of flux along the axon with the transmural flux through the axonal walls



**Figure 1:** Diagram showing the axons passing from the eye into the optic nerve. Note that the axons are well spaced within the eye, whereas they form a tightly packed bundle in the optic nerve. Figure taken from Band et al. (2009).

and using Poiseuille's law for flow along the axons, we obtain a simple differential equation for the pressure changes along each axon in the eye. Assuming that the axons are tightly packed in the optic nerve so that fluid leaks directly from one axon to its neighbours, we can similarly construct a partial differential equation for the fluid pressure in the region of the optic nerve. Applying the continuity of pressure and flux at  $z = 0$  and appropriate boundary conditions, we obtain a complete mathematical problem. This depends on a number of dimensional parameters including the pressure in eye,  $p_e$ , and the pressure in the cerebrospinal fluid (CSF),  $p_c$ .

Interestingly, nondimensionalisation allows us to scale  $p_e - p_c$  out of the system and we find that the dimensional rate of flow is always directly proportional to the pressure difference between the eye and the CSF. We are also able to find closed-form solutions for  $p_+(r, z)$  and  $p_-(r, z)$  in terms of Bessel functions.

### 3 Results

Our solutions indicate that the passive flux in the optic nerve is greatest near  $z = 0$  and  $r = a$  (i.e. at the periphery of the optic nerve, near the lamina cribrosa). Using realistic parameter values for a glaucomatous patient with an intraocular pressure of 30 mmHg, we find that the Péclet number for ATP is greater than one in a zone that extends almost  $5 \mu\text{m}$  into the optic nerve and more than 10 mm along it. In this region, advection of ATP will dominate over diffusion and the axons could quickly become depleted of ATP, causing an interruption of AAT and ultimately cell death.

Initially, the dead axons remaining on the periphery of the nerve would protect the inner axons. However, as the dead axons decay, new axons will be exposed to the elevated PNIFP and the gradual neuropathy will continue. Thus, our proposed mechanism is able to explain both the changes to AAT observed in animal models and the slow progression of cell death from the outside of the optic nerve inwards. Further work needs to be done to verify this model experimentally. Although challenging, it should be possible to test our hypothesis by directly measuring pressure and flow within the optic nerve.

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