PERSPECTIVE

A hypothesis to explain ganglion cell death caused by vascular insults at the optic nerve head: possible implication for the treatment of glaucoma

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Some apparent characteristics of ganglion cell death in glaucoma

Glaucoma is a progressive optic neuropathy with characteristic optic disc changes and associated visual field defects.^{1,2} The pattern and progression of visual field loss due to ganglion cell death varies between glaucoma patients suggesting that there is some variability in the magnitude of the insult responsible for the cell loss. Ganglion cell death with a spatial and temporal distribution typical of "glaucoma" can be experimentally induced in animals.³⁻⁵ One way to try and mimic glaucoma in experimental animals is to raise the intraocular pressure (IOP).³⁻⁶ It is clear from such studies

that ganglion cells do not all die at the same time.⁴⁻⁸ Furthermore, the rate of deterioration of ganglion cells is proportional to the magnitude of the insult.⁹ The reason for the initiation of ganglion cell death in glaucoma is unknown, but a number of explanatory theories have been proposed with the vasogenic theory perhaps the most widely accepted hypothesis.^{2,10-12}

Oligaemic/hypoxic insult to the optic nerve head leads to ganglion cell death in glaucoma

Raised IOP is not the sole factor responsible for glaucomatous retinal damage but an important one of a number that have been implicated (Fig 1).¹²⁻¹⁷ Only 10% of patients

Figure 1 Possible causes of ganglion cell death in glaucoma. It is suggested that activation of sufficient risk factors causes the quality of blood supply in the optic nerve head to be affected. As a result, the nutritional supply to the optic nerve head is slowly compromised (oligaemia/hypoxia) particularly affecting astrocytes, microglia, and ganglion cell axons. Even the central retinal artery/vein may become slightly affected. Such insults eventually lead to the death of ganglion cells as depicted and detailed in Figures 2 and 3. One may also envisage other modes of stimulating ganglion cell death in glaucoma (lighter blue boxes) where the vascular system does not have a direct role. Some of these possibilities may also be linked to certain risk factors, but these are not indicated.

with increased IOP (≥ 22 mm Hg) have glaucoma and between one third and one half of patients with glaucoma initially do not have elevated IOP.^{1 18 19} Furthermore, as many as one sixth of patients with glaucomatous damage do not appear to have elevated IOP.¹ It is therefore clear that raised IOP is not synonymous with having glaucoma.^{1 20 21} Nevertheless, high IOP is arguably the most important *risk factor* (see Fig 1), and it is clearly associated with ganglion cell death in glaucoma patients.

As recently stated by Hayreh,¹² "evidence has progressively accumulated to suggest that vascular insufficiency at the optic nerve head plays an important role in the pathogenesis of glaucomatous optic neuropathy and that glaucomatous optic neuropathy is a multifactorial disease." A strong case has been made out to support the view that an alteration in the *quality of blood supply* in the optic nerve head can lead to glaucoma.^{12 17 22-32} The main blood supply to the optic nerve head is from the posterior ciliary artery via the peripapillary choroid and short posterior ciliary arteries or the circle of Zinn-Haller.²⁶ It is the quality of the blood supply from these vessels that may be particularly affected, rather than the blood flow in the central retinal artery. An alteration in the quality of blood supply in the optic nerve head capillaries could be indirectly triggered to a greater or lesser extent by increased IOP (due to collapse of the lamina cribrosa?), abnormal blood pressure, altered rheological characteristics of the blood, local vasospasm, possibly haemorrhage, autoregulatory defects, or changes in the physiological and/or physical characteristics of the blood vessels in question. Should this occur then the tissues in the optic nerve head might suffer oligemic and/or hypoxic insults because the local oxygen supply would be altered. It is of interest to note that in experimental studies a decrease in ocular (particularly uveal) blood flow occurs when the IOP is elevated.^{33 34} There is, however, no good evidence to show that elevated pressure directly influences blood flow in the region of the lamina cribrosa although it has been proposed that blood flow regulatory mechanisms may be faulty in this region in glaucoma.³⁵⁻³⁷ It seems reasonable, therefore, to hypothesise that an alteration in the quality of the blood supply in the microcirculation of the optic nerve head caused by direct and indirect actions of a combination of risk factors leads to an oligemic/hypoxic insult. This then contributes to ganglion cell death (with the initial insult being at the axonal level at the optic nerve head) in certain glaucoma patients.^{17 22 25 38} Unfortunately no satisfactory method exists to measure the blood dynamics in the optic nerve head of glaucoma patients to demonstrate whether oligemia/hypoxia occurs.

A hypothesis to explain how differential ganglion cell death may occur

Both visual field loss^{39 40} and neuroretinal rim loss⁴¹ appear to follow typical patterns in glaucoma, which would imply that certain ganglion cells are more susceptible than others. Also, a preferential loss of ganglion cells in the peripheral retina seems to occur in experimental glaucoma both in monkeys⁴² and rats.⁷ It would appear, therefore, that a differential rate of death of ganglion cells occurs. One explanation is that a greater rotation or disruption of the cribriform beams at the periphery of the optic disc accounts for a periphery to centre progression of visual field loss in glaucoma. However, some evidence exists to suggest that axons from peripheral and central areas of the retina may randomly pass through peripheral or central parts of the optic nerve (see Morgan¹¹), which argues against a close correlation between the pattern of visual

field loss in glaucoma and the anatomical position of ganglion cell axons at the optic nerve head. We previously proposed⁴³ that the specific pattern of ganglion cell death in glaucoma (differential ganglion cell death) could be influenced by the repertoire of inhibitory and excitatory receptors associated with each ganglion cell. In the present review, we hypothesise that both the axonal injury at the optic nerve and the repertoire of inhibitory and excitatory receptors of each ganglion cell have a major role in determining the cell's fate in glaucomatous neuropathy.

Should oligemia/hypoxia occur in the optic nerve head how could it lead to a similar but not identical pattern of ganglion cell loss in glaucoma patients? One such proposal is outlined in Figure 2. Components that are likely to be affected include ganglion cell axons, astrocytes, microglia, and the lamina cribrosa.⁴⁴⁻⁴⁷ A sustained (or intermittent) oligemic/hypoxic insult to such components before loss of ganglion cell function may contribute to the "cupping" associated with glaucoma. It is of importance to note that glaucomatous visual field abnormalities have been reported to precede structural changes of the optic nerve head and nerve fibre layer.⁴⁸⁻⁵² Structural changes at the optic nerve head may therefore be apparent before total loss of ganglion cell function, supporting the opinion that the initial insult in glaucoma occurs at the optic nerve head and that the death of the ganglion cell soma is not the cause for the "cupping." An increase in the intracellular calcium concentration in ganglion cell axons as a result of oligemia/hypoxia may trigger disruption of axonal transport and cytoskeletal breakdown as demonstrated in isolated optic nerves under hypoxic conditions.⁵³ Sustained or intermittent insults to groups of astrocytes in the optic nerve head region could also cause them to become "reactive," change shape, possibly swell,⁵⁴ and even die. Astrocytes in the lamina cribrosa and prelaminar region of the optic nerve head provide structural and cellular support and participate in forming the extracellular matrix.^{11 47} After an oligemic/ischaemic insult at the optic nerve head, astrocytes may become "reactive" eliciting a variety of possible effects. These may include disrupting axoplasmic transport, initiating changes in cribriform physiology and biochemistry, alterations in matrix modelling and the release of potential toxins (nitric oxide, tumour necrosis factor α , transforming growth factor β , glutamate); all contributing to the characteristic form of glaucomatous optic neuropathy.^{47 55-60} Moreover, D-serine may be released from stressed astrocytes to potentiate the agonistic effect of glutamate at NMDA receptors,⁶¹ so exacerbating ganglion cell injury. It should be noted that optic disc "cupping" has been reported in other conditions leading to optic nerve head ischaemia, such as compressive optic neuropathy, anterior ischaemic neuropathy, and Leber's optic neuropathy,⁶²⁻⁶⁵ although it may not be a consistent feature. A recent population study revealed that "cupping" of the optic nerve head is found in 92% of eyes with arteritic anterior ischaemic optic neuropathy and in 2% of eyes with non-arteritic anterior ischaemic optic neuropathy.⁶³ The reasons for the low incidence of "cupping" in non-arteritic anterior ischaemic optic neuropathy are unknown, but it has been proposed by Hayreh⁶⁶ that the ischaemic process may not be as marked and massive as in arteritic anterior ischaemic optic neuropathy. It may well be that similar alterations in the *quality of the blood supply* to certain regions of the optic nerve head develop both in glaucoma (in a chronic, slowly progressive way) and arteritic anterior ischaemic optic neuropathy (in an acute, rapidly progressive way) leading to a similar, although not identical, "cupping" of the optic disc.

Astrocytes are abundant in the optic nerve head as well as throughout the remainder of the retina and have the

Figure 2 A hypothesis to explain ganglion cell death in glaucoma. Various components in the optic nerve head may be affected by oligoemia/hypoxia as a result of an alteration in the microcirculation (see Fig 1). While the ganglion cell axon may be affected in the initial stages of the insult, the whole of the cell will eventually suffer (exist at a lower homeostatic state) with glutamate particularly being "non-physiologically" released into the extracellular space (Fig 3). Astrocytes and microglial cells are also likely to release a variety of substances into the extracellular space after an undefined duration of insult. Some of these substances may have "protective" properties while others will have adverse effects on neurons. Moreover, increased levels of glutamate in the extracellular space are potentially toxic to many retinal cells. Müller cells will as a consequence become particularly active in an attempt to maintain physiological levels of extracellular neurotransmitters. However, the excessive demands placed on Müller cells will eventually lead to them becoming inefficient. This will result in a slow but gradual rise in the level of glutamate and other neurotransmitters (for example, GABA) in the extracellular space. The ganglion cells, being at a lower homeostatic status than other retinal cell types will potentially, therefore, be more susceptible to this extracellular rise of neurotransmitters. It is proposed that at a certain point, glutamate will overexcite ganglion cells to initiate a dying process. It is also hypothesised that the variability in the death rate of individual ganglion cells will depend on the degree of this overexcitement, which is dependent in part on the number of excitatory and inhibitory receptors associated with the neuron (and also upon a rise in the extracellular levels of neurotransmitters). Activation of inhibitory GABA receptors, for example, will hyperpolarise the cell and this will tend to counteract the overexcitation.

capacity to communicate with their respective neighbouring astrocytes via gap junctions^{47 67 68} as well as with Müller cells.⁶⁹ Astrocytes therefore have the capacity to communicate with other glial cells throughout the retina. An insult in the form of reduced energy to a collection of these cells in the optic nerve head may theoretically, then, be signalled to many other retinal astrocytes. Studies on cultures of astrocytes strongly support this view.⁵⁷ An oligoemic/hypoxic insult to the optic nerve head may cause *depolarisation* of “local” astrocytes possibly leading to a form of spreading depression.⁷⁰ Spreading depression was originally described by Leão⁷¹ as a stereotypic response of nervous tissue to a variety of noxious influences. In isolated chick retinas, the propagation of spreading depression occurs in circles with a velocity of 1–10 mm/min and accompanying voltage changes can be detected from the ganglion cells to the photoreceptors.⁷⁰ Astrocytes are thought to play a major part in the process of spreading depression in the retina with potassium, calcium, and other substances which include glutamate being involved.^{72 73} Spreading depression is known to increase glucose consumption and to place an additional energy demand upon cells. It has also been demonstrated to occur in brain tissues during hypoxia.^{74 75} Thus, oligoemia/hypoxia to the optic nerve head may cause astrocytes in this region to no longer function efficiently—for example, they may become unable to maintain the correct ionic homeostasis or to communicate information to regions outside the retinal optic nerve head area. They may also release, as already mentioned, substances such as nitric oxide,⁵⁸ prostaglandins,⁵⁹ glutamate,⁵⁷ or other factors⁶⁰ into the extracellular milieu, which could exacerbate injury to ganglion cells and other neighbouring structures such as microglia and the lamina cribrosa. Stressed microglia may also release a variety of substances.⁷⁶ It is plausible to conclude, therefore,

that an insult originating at the optic nerve head can to some degree be transmitted, over a variable period of time, to much of the retina. Moreover, substances released from stressed astrocytes and microglia, in particular in the optic nerve head region, could add to the general malaise of ganglion cells. These ideas are based mainly on studies on cultured cells as information on the intact retina is lacking.

A deficit in the supply of energy to ganglion cell axons due to oligoemia/hypoxia is likely to gradually extend in both a retrograde and an orthograde manner (see Fig 3). A variable reduction of energy (ATP) is likely therefore to exist in the ganglion cell over time with the greatest effect being in the optic nerve head region. The lamina cribrosa of the optic nerve head is likely to be at risk because of the transition between an efficient (myelinated axons) and not so efficient (unmyelinated axons) energy system of action potential transmission. This is supported by histochemical studies on the human optic nerve to strongly support the view that the unmyelinated laminar and prelaminar portions of the optic nerve have greater demands for mitochondrially derived ATP than the myelinated postlaminar segment⁷⁷ and as a consequence could be more susceptible to an energy deficit. This may cause a reduced normal resting membrane potential with homeostasis of the ganglion cells now maintained at a lower status so making them more susceptible to further insults. This is similar to that which may occur in ageing.⁷⁸ Since ganglion cells are laden with glutamate, it is suggested that at a lower homeostatic state there will be a tendency for some glutamate to “leak out” into the extracellular space, the rate of leakage being dependent on the energy status of the cell. Increased extracellular glutamate (originating from ganglion cells functioning at a reduced homeostasis and also possibly from astrocytes) will, over time, become toxic to neurons containing specific types of glutamate receptors

Figure 3 Proposed stages for ganglion cell death in glaucoma (see Figure 2 for details).

(ionotropic AMPA/kainate and NMDA receptors).⁶ The rate of take up of glutamate and subsequent metabolism and redistribution by the Müller cells will need to be increased in order to maintain non-toxic levels of glutamate in the extracellular space.^{79–80} Müller cells would therefore be functioning overtime, perhaps accelerating ageing. Uptake and metabolism of glutamate are energy dependent processes and the energy demands placed on the Müller cells will be significant. It is postulated that after a time Müller cell functions will become less efficient and when this occurs the extracellular glutamate concentration will slowly rise. While a small rise may not in itself be toxic to healthy retinal neurons it may be toxic to ganglion cells already at a lower homeostatic state (see Clarke *et al*⁸¹). Inefficient uptake processes associated with Müller cells will eventually cause a slight rise in extracellular levels not only of glutamate but also of other neurotransmitters such as GABA. The prediction therefore is that certain Müller cell functions in glaucoma become inefficient (but not dysfunctional) with time. It is generally believed that the flash electroretinograms, and specifically the b-wave amplitude, from glaucoma patients are unaffected, which is consistent with this idea. It is worthy to note, however, that recent reports have shown a reduction of a-wave amplitude⁸² and a delay in b-wave implicit times⁸³ in the dark adapted flash electroretinograms (ERGs) from patients with advanced glaucoma. Interestingly, the b-wave amplitude of the ERG is slightly reduced with ageing⁸⁴ and glaucoma has been described as an “ageing disease.” Inefficient function of Müller cells and subsequent elevation of extracellular neurotransmitter levels may now result in neuronal receptors being stimulated in a non-physiological manner. Also, the extracellular neurotransmitters may find a route to the vitreous humour, although one would imagine that elevated levels of glutamate in the vitreous humour would only be detectable at the most advanced stages of glaucoma. It is important to note that, in the vitreous humour of glaucoma patients, levels of the major retinal neurotransmitter glutamate⁸⁵ have been reported to be elevated.⁸⁶ Moreover, experimental evidence exists to show that Müller cells are affected in a monkey glaucoma model.^{87–88}

It has been postulated that a small rise in extracellular glutamate will cause overstimulation of ionotropic glutamate receptors⁸⁹ which are expressed throughout the retina.⁹⁰ It is conceivable that certain ganglion cells will be particularly susceptible to this neurotoxic phenomenon because they are at a lower homeostatic state compared with other neurons because of oligoemic/hypoxic insults to their axons in the optic nerve head region. Stimulation of glutamate receptors leads to depolarisation and uncontrolled or excessive depolarisation may cause cell death.⁸⁹ A small but maintained rise in the extracellular levels of the two major retinal neurotransmitters, glutamate and GABA, could provide a simple explanation for the variation in ganglion cell death timing.⁴³ The repertoire of receptors associated with ganglion cells is known to vary. These cells express glutamate and GABA receptors. Activation of two of the three types of GABA receptor in ganglion cells (GABA_A and GABA_B) causes hyperpolarisation^{91–92} while activation of ionotropic glutamate receptors (NMDA, kainate, and AMPA) leads to depolarisation.⁹³ Excessive or uncontrolled depolarisation of neurons leads to cell death and this is triggered by an initial influx of sodium and calcium ions.^{6–43} Furthermore, the degree of depolarisation of any single ganglion cell will depend upon the numbers and types of GABA and glutamate receptors associated with that cell. We suggest, therefore, that a ganglion cell expressing a defined number of excitatory (for example, glutamate) receptors will theoretically be more susceptible than a similar cell expressing the same

excitatory receptors plus some inhibitory (for example, GABA) receptors.⁴³ Inhibitory and excitatory receptors associated with ganglion cells are not exclusively GABAergic and glutamatergic, respectively. Inhibitory receptors include those responsive to adenosine (A₁ type), serotonin (5-HT_{1A} type), and noradrenaline (α_2 adrenergic type) while excitatory receptors include the nicotinic acetylcholine type. There is reasonable evidence to suggest that ganglion cells contain nicotinic,⁹⁴ adenosine,⁹⁵ and α_2 adrenergic⁹⁶ receptors.

It is important to emphasise that this theory suggests that initial insults to all or most of the ganglion cells in glaucoma occur on their axons in the optic disc head region and that the rate of individual ganglion cell death would be further determined by the receptor profile associated with the ganglion cell body and dendrites (Fig 3). Thus the axon (in the optic nerve head region in particular) of a dying ganglion cell in glaucoma is predicted to be at a more advanced stage in the death process than the cell body. This may be compared with a dying ganglion cell in retinal ischaemia (for example, central retinal artery occlusion) where deterioration of the ganglion cell body is at a more advanced state than within the axon. It is also suggested that the cascade of events that leads to ganglion cell death in glaucoma as proposed proceeds at a very slow and variable rate depending on the nature of the oligoemic/hypoxic insult to the optic nerve head. The insult may either be gradual, continuous, or variable in intensity and may occur over many years.

Putative ways for reducing the rate of ganglion cell death

A number of putative therapeutic strategies are summarised in Table 1. Stopping whatever risk factor(s) cause(s) the oligoemic/hypoxic-like insult in the optic nerve head would be hypothesised to be an ideal way to attenuate ganglion cell death. If instances were found where raised IOP was identified as the major cause of the insult, then reducing IOP either by surgery or with a pharmacological agent would be the ideal approach (see Osborne *et al*⁶). Lowering IOP, nevertheless, often proves beneficial even in patients with normal tension glaucoma,^{97–98} suggesting that there is a level of “tolerable” IOP which depends on other accompanying factors, such as the quality of blood supply to the optic nerve head. In such cases, one approach might be to correct whatever causes the change in the quality of blood supply in the microvasculature of the optic nerve head. This could mean simply increasing blood flow in the optic nerve head, assuming such a strategy is feasible. Until it is possible to establish reasons for any alterations in the quality of the blood supply in the optic nerve head, it will be difficult to devise an appropriate treatment. The term *vasoprotection* has been coined in this connection.⁹⁹

The term *neuroprotection*, in the context of glaucoma, implies that an agent reaches the retina and slows down the cascade of events leading to ganglion cell death.^{6–43} A number of substances have been shown to attenuate ganglion cell death in animal experiments. These include certain neurotrophins, NMDA receptor antagonists, free

Table 1 Summary of possible pharmacological ways to attenuate ganglion cell destruction as suggested in Figures 2 and 3

- Counteract risk factor in question—eg, lower raised IOP
- Maintain normal blood supply to optic nerve head
- Prevent hypoxic/oligoemic insult to ganglion cell axons
- Prevent substance release from astrocytes/microglia that may affect ganglion cell survival
- Maintain optimum functioning of Müller cells
- Prevent glutamate toxicity to retinal neurons
- Prevent excessive depolarisation of ganglion cells
- Administration of neurotrophic factors

radical scavengers, calcium channel blockers, α adrenoceptor agonists, betaxolol, and nitric oxide synthase inhibitors.¹⁰⁰ Neurotrophins, for example, protect ganglion cells because their endogenous supply is partially or completely reduced by a disruption of the retrograde transport process associated with ganglion cell axons.¹⁰¹ It remains to be investigated whether a drug that stops spreading depression will benefit glaucoma patients. It is known that some compounds (such as MK-801) are able to inhibit retinal spreading depression associated with astrocytes⁷⁰ and can also protect against ischaemia induced damage.^{102–104}

Pharmacological agents which counteract changes to optic nerve head astrocytes caused by an oligoemic/hypoxic insult may also benefit glaucoma patients. Support for this idea comes from the work of Neufeld and collaborators.⁵ They have showed that nitric oxide synthase is altered in optic nerve head astrocytes in both glaucoma patients and also in animals following a sustained elevation of IOP. Moreover, treatment of animals with a nitric oxide synthase inhibitor attenuated the ganglion cell death induced by sustained elevated IOP.⁵ Excessive production of nitric oxide by “reactive” astrocytes in the optic nerve head has been proposed to have a major role in axonal degeneration.⁵⁸

To attenuate ganglion cell death in glaucoma patients it is necessary to have agents that particularly protect the axon and, secondly, the cell body. Studies on isolated optic nerves have shown that voltage sensitive sodium channel blockers^{105–106} and drugs which prevent the reversal of the sodium/calcium exchanger^{106–107} attenuate anoxia induced death of ganglion cell axons. In this respect, it is of interest to note that a number of β adrenoceptor antagonists currently used to lower IOP in glaucoma patients can reduce certain cation influx into neurons by directly interacting with specific sodium or calcium voltage gated channels.^{108–109} There is no evidence that any of the other antiglaucoma drugs behave similarly. Of the β blockers tested, betaxolol displays the most potent sodium and calcium blocking activity and these properties may be related to its ability to partially counteract ganglion cell death in rats and rabbits induced by raised IOP.^{110–111} Agents which reduce excessive depolarisation occurring subsequent to proposed Müller cell inefficiency may also be used to protect overall ganglion cell function. Substances that may be of use include excitatory receptor antagonists, inhibitory receptor agonists (α_2 adrenoceptor agonists), and voltage sensitive sodium or calcium channel blockers. Support for this view comes from experimental studies where glutamate receptor antagonists such as MK-801,¹⁰² mepantrine¹¹² and dextromethorphan,^{113–114} inhibitory receptor agonists such as R-PIA (adenosine A₁ receptor agonist),¹¹⁵ brimonidine,¹¹⁶ and clonidine,¹¹⁷ and voltage sensitive calcium channel blockers^{118–119} all reduce retinal damage induced by raised IOP.

Attenuation of ganglion cell death can theoretically, therefore, be implemented by slowing down the biochemical events that follow depolarisation/excitotoxicity induced insults.^{6–43} This would also be achieved by using free radical scavengers, for example. Numerous laboratory studies have showed that ischaemia induced destruction of animal ganglion cells can be attenuated in this manner.^{120–123} In glaucoma, however, it should be borne in mind that the ganglion cell axon is proposed to be at a more compromised state than the rest of the ganglion cell while in ischaemia, for example, this is not the case. Agents, therefore, that are targeted to protect the ganglion cell generally by preventing excessive depolarisation (for example, NMDA antagonists, GABA agonists) without paying particular attention to the axon may not be the ideal drugs for use in glaucoma.

Yet another theoretical approach to attenuating ganglion cell death in glaucoma would be to maintain the optimum health and functioning of Müller cells for as long as possible after the hypothesised initial insult in the optic nerve head. Evidence from the basic sciences suggests that altered Müller cell function exacerbates ganglion cell death¹²⁴ so this approach is worthy of pursuit. Agents that stimulate glycogenolysis or glutamate transport and metabolism in the Müller cells may prove beneficial in this respect.

Conclusions

Despite the quantities written about glaucoma, definitive data on the subject are sparse. The disease(s) is/are characterised by a defined optic neuropathy with a progressive loss of vision that is of a specific pattern. We hypothesise, therefore, that ganglion cell axon injury caused by oligoemic/hypoxic insults to components in the optic nerve head could ultimately lead to an insult at the level of the ganglion cell body and dendrites owing to inefficient Müller cell function. We also hypothesise that Müller cells and astrocytes play an important part in this whole process with the latter cell type particularly contributing to the cupping associated with glaucoma. For a substance to effectively protect the ganglion cell in glaucoma it should have an action on the ganglion cell axon and, secondly, the rest of the cell. However, such a substance may not be effective enough to have a measurable neuroprotective effect for glaucoma patients unless some of the other proposed processes contributing to ganglion cell death are blunted (Fig 2). It is therefore suggested that the way forward to treat glaucoma would be to use a cocktail of substances, which when administered would reach the retina, and in doing so protects not only the ganglion cells, particularly their axons, but also, for example, maintain optimum functioning of the Müller cells, and counteract any negative physiological and pharmacological effects from the astrocytes and/or microglial cells.

The present article is an attempt to provide an explanation as to how ganglion cells may be initiated to die in glaucoma, so as to develop therapeutic strategies for the treatment of the disease. It is not meant to contradict ideas put forward by other authors but more to serve for debate and stimulate future research. Definitive data about ganglion cell death in glaucoma are sparse and consequently many of the ideas for the proposed theory are derived from general studies on nervous systems. We nevertheless feel that the hypothesised approach has merit even though caution is necessary. We are of the opinion that the slow progression of glaucoma does provide scientists and clinicians with the real possibility of slowing down the rate of ganglion cell death and to develop a pharmacological means of doing so warrants a working hypothesis. For this idea to become feasible, it will also probably be necessary to develop procedures to enable delivery of the “neuroprotectant” to the retina. There is a need to remain optimistic despite the lack of success in finding similar ways to slow down the rate of neuronal death in other diseases of the central nervous system. The implication from the theory proposed is to suggest that pharmacological agents that act solely at the ganglion cell level (Fig 3) may not be sufficient for effective neuroprotection in glaucoma and that only by blunting several of the other negative processes involved in the disease (Figs 1 and 2) will real progress be made.

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