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Some current ideas on the pathogenesis and the role of neuroprotection in glaucomatous optic neuropathy

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ABSTRACT. *The primary features of glaucomatous optic neuropathy are characteristic changes in the optic nerve head, a decrease in number of surviving ganglion cells and a reduction in vision. It is now generally accepted that a number of factors, including elevated intraocular pressure, could lead to the changes seen in the optic nerve head and to obtain a pharmacological means to treat the causes will vary from patient to patient. In contrast, a cascade of events have been proposed to explain how the changes in the optic nerve head may lead to the slow and differential death of ganglion cells in the disease. It is also proposed that drugs (neuroprotectants) influencing this cascade of events can attenuate ganglion cell death and lead to the treatment of all glaucoma patients.* Eur J Ophthalmol 2003; 13 (Suppl. 3): S19-S26

KEY WORDS. *Glaucoma, Optic neuropathy, Ganglion cell death, Neuroprotection*

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INTRODUCTION

The World Health Organisation estimates that worldwide there are 105 million people with glaucoma of whom around 5 million are blind (1). Even in the developed world, where attempts at early diagnosis are more established, there is little sign that the problem is diminishing. In the United States of America, glaucoma accounts for 10% of all recorded cases of blindness (2). Approximately, 3-5% of White Americans, 10% of African Americans and 20% of Afro-Caribbeans over the age of 70 years of age have open angle glaucoma (3).

Glaucomatous optic neuropathy (GON) may be defined as a progressive optic neuropathy characterized by structural damage to the optic nerve head and death of retinal ganglion cells. There is a similar resultant pattern of visual field loss in GON patients suggesting that certain ganglion cells are more susceptible than others. The progression of visual field loss varies between patients indicating that there might be some variability in the magnitude of insult responsible for cell loss in glaucoma.

Elevated intraocular pressure (IOP) is associated with as many as five sixths of glaucoma patients (4) but fewer than 10% of patients with increased IOP (> 22mm Hg) have glaucoma (3,5) There are cases where an acute elevation of IOP (often termed acute glaucoma) does not lead to the typical ophthalmological appearance of GON. The term “glaucoma” is therefore only applied to those individuals that also display the characteristic optic neuropathy. In addition, in many instances where the IOP has been lowered in GON patients the measurable beneficial effects have often been difficult to detect suggesting that raised IOP is not the sole cause for GON.

Notions regarding the pathogenesis of GON remain speculative and there is now an increased opinion that there is no uniform cause for GON, but that it rather represents the clinical face of a multifactorial disease

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(6-9). We have suggested, along with others, that the cause for the optic disc being affected in a defined way may be variable, but also that the processes that then lead to the eventual death of ganglion cells may follow a more uniform pattern (9-13). Thus in some instances the cause leading to the changes seen in the optic nerve head may be due to defined genes being affected. In other instances patients are susceptible to raised IOP for some reason or another. In yet other instances an abnormal metabolism may be the cause. Treating therefore the possible cause(s) that lead to changes seen in the optic nerve head of individual GON patients (such a mode of treatment has been termed "indirect neuroprotection of ganglion cells") may therefore be variable and be more of a challenge than using a drug that influences the subsequent cascade of events that lead to ganglion cell death (termed "direct neuroprotection of ganglion cells") which could be similar in all GON patients. Predicting the cascade of events that lead to ganglion cell death following changes seen in the optic nerve head of GON patients is therefore a challenge as it could lead to the development of a suitable neuroprotectant for all GON patients (12).

Potential causes to induce the changes seen in the optic nerve head

Some potential events that may lead to the changes seen in the optic nerve head of GON patients are shown in Figure 1. The reason why some of these causes are considered a possibility will now be briefly discussed.

Raised IOP. The majority of patients with primary open-angle glaucoma have an elevated IOP, and all patients with secondary glaucoma have an elevated IOP; therefore, a raised IOP, until recently was a defining characteristic of GON. However, the occurrence of GON without an elevated IOP (normal tension glaucoma) has been known for over a century, (14) and is now a well-described entity, accounting for approximately 15% of all cases of GON (3). Moreover, only 1% of patients with ocular hypertension develop GON each year (15), and once developed, the level of IOP alone does not separate patients with stable visual fields from those with progressive field loss (16). Conversely, a body of evidence, recently supported by data from prospective studies, indicates that reducing the IOP in a patient with glaucoma retards the rate of visual field loss (17-19, 20). Furthermore, the preponderance of evidence indicates that the lower the pressure, the slower the rate of visual field loss (18). Interestingly, this is true even if the starting pressure is low (19). Although there is no doubt that IOP plays a causal role in GON, the manner by which an elevated IOP causes the typical changes seen at the optic nerve head remains a mystery.

IOP-induced mechanical injury to the optic nerve head

Several studies have shown that the lamina cribrosa can be structurally disrupted by an elevated IOP with displacement of the optic nerve head (21-23). At the micro-anatomical level, mild mechanical injury causes cytoskeletal alterations in axons and loss of microtubules (24,25). This may partly explain why acute elevations of IOP impede retrograde axonal transport, resulting in reduced amounts of brain-derived neurotrophic factor reaching the ganglion cell bodies (26,27). This loss of trophic support may play an important role in ganglion cell death (26). Recently, pressure-induced functional changes have been demonstrated in the glial cells of the optic nerve head (the major cellular component of this region) (28,29). The release of degradative substances from pressure-activated astrocytes may cause tissue remodeling and play a central role in the pathogenesis of GON (29). Apart from the direct mechanical effects on neural and glial tissue, an elevated IOP may affect optic nerve head microvasculature.

It is possible that the primary defect at the optic nerve head is a pressure-induced disruption of the capillary network causing ischemia and a secondary loss of axons. Microvascular changes have been noted in glaucomatous eyes (30); however, there is no difference in the number of capillaries per unit volume between normal and glaucomatous eyes (31,32). Furthermore, in monkey eyes with experimental glaucoma, the loss of vascular and neural tissue occurs at the same rate, so the proportion of vascularized tissue remains stable (33). Hence, there is no experimental evidence to suggest that pressure-induced loss of capillaries in the optic nerve head is a primary event in GON. However, there is considerable evidence that reduced blood flow at the optic nerve head plays a role in GON.

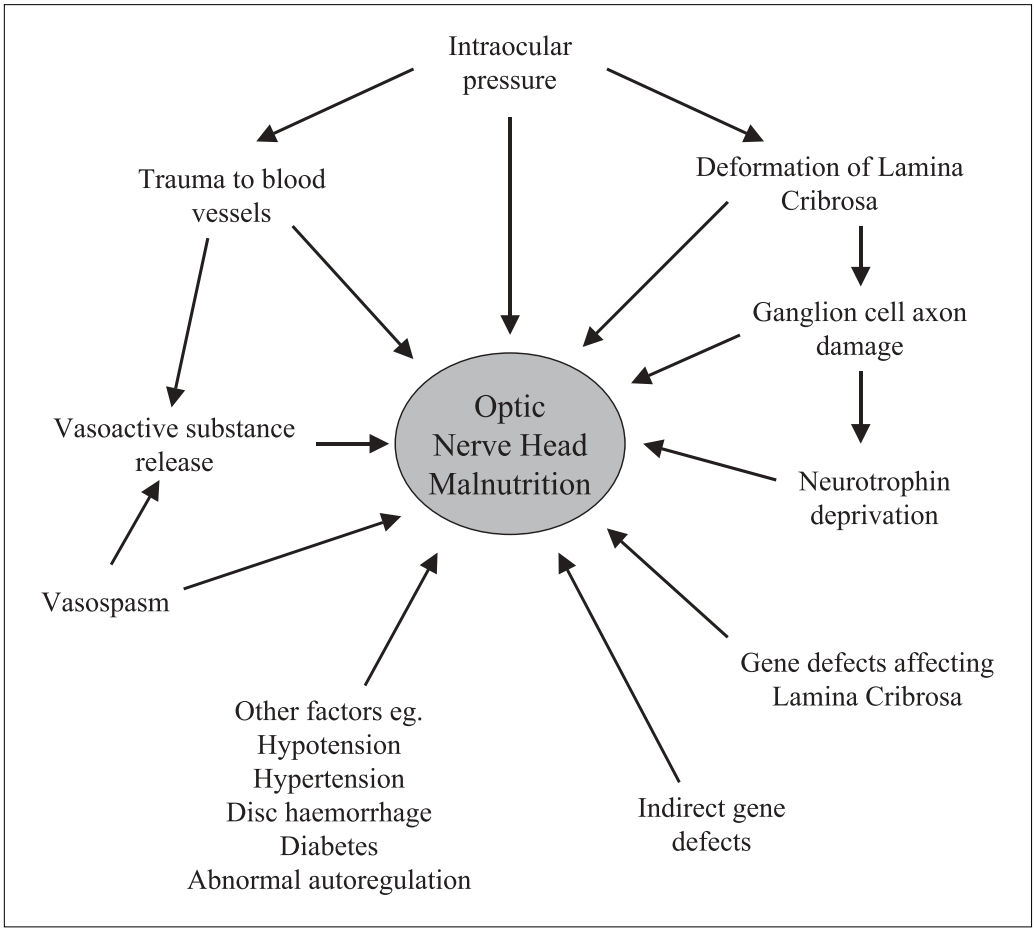

Fig. 1 - *Some possible causes of initial insult to the optic nerve head in different glaucoma patients.*

IOP-induced reduction in optic nerve head blood flow

Ocular blood flow is directly related to the perfusion pressure (arterial pressure minus venous pressure) and inversely related to the resistance in the capillaries (34). An elevated IOP reduces perfusion pressure by raising venous pressure at the exit point from the eye; however, blood flow may not be affected if the vascular resistance is lowered in compensation. Even a normal IOP reduces the maximal possible perfusion pressure because the normal IOP usually exceeds orbital venous pressure. Hence, a critical determinant of ocular blood flow is the control of vascular resistance (autoregulation). The combination of reduced perfusion pressure and suboptimal autoregulation would leave the optic nerve head and retina particularly vulnerable to ischemic injury.

There is considerable evidence to support the notion that vascular factors play a role in GON. Healthy young humans and primate models maintain blood flow over a wide range of IOP by successful autoregulation (35, 36); however, glaucoma patients have an abnormal autoregulatory capacity (37-39). Abnormal autoregulation is also found in elderly patients and atherosclerotic monkeys (40, 41). Therefore, an IOP-induced reduction in perfusion pressure may be a critical component in the pathogenesis of GON.

Perfusion pressure may also be affected on the arterial side. Nocturnal hypotension, in association with local and systemic risk factors, has been associated with GON (42, 43). Epidemiological studies have reported a relatively weak association between the risk factors for cardiovascular disease (eg: age, hypertension, and diabetes) and GON (44-46). Vasospasm, however, appears to be an important risk factor for GON, especially the normal tension glaucoma (47, 48).

Purely vasogenic GON

Experimental evidence supports the notion that chronic ischemia at the optic nerve head (induced by chronic endothelin exposure) can produce axonal loss and the typical features of GON in the presence of a normal IOP. Hence it is conceivable that GON could result from a purely vasogenic problem in the absence of an elevated IOP. However, it should be remembered that even a normal IOP challenges the optic nerve head autoregulatory mechanism, and it has been clearly demonstrate that a 30% reduction in IOP retards visual field loss in patients with normal tension glaucoma. Purely vasogenic GON, therefore, may not be a common clinical entity.

Perhaps the most attractive concept concerning the pathogenesis of GON combines mechanical and vascular aspects. It has been proposed that these aspects produce clinically distinct patterns of GON (49), although pure forms are uncommon (50, 51). GON can be generalized, with diffuse field defects and concentric cupping, or focal, with localized optic disc changes and associated field defects, or a combination of both. The diffuse component of the visual field damage is related to IOP (49), whereas the localized component is only weakly related to IOP (52). Similarly, focal optic disc changes tend to show a weak association with IOP, but a strong asociation with vascular dysregulation; and concentric cupping tends to be associated with a high IOP, but normal vasculature (50).

From optic disc head changes to ganglion cell death in glaucoma

It has been proposed, that in most cases of glaucoma, there is impaired delivery of nutrients, such as oxygen and glucose, to the optic nerve head (53). This is due to ischemic-like insults (hypoxia/anoxia/ oligomia) caused by a compromise in the blood flow associated with the optic nerve head. Components likely to be affected will include the lamina cribosa, ganglion cell axons, astrocytes and blood vessels. Moreover, altered delivery of neurotrophin support may occur (26). The severity of the impairment of nutritional supply may or may not increase with time. With the progress of time it is likely that other areas of the retina will eventually become secondarily affected by a stressed metabolism. Moreover, at some stage, Müller cell function will become inefficient and this will result in an elevation of extracellular levels of glutamate and other neurotransmitters (54). Glutamate is known to be particularly toxic to ganglion cells initiating death by interacting with specific receptors present in variable amounts on ganglion cells (10). Thus high levels of extracellular glutamate would kill ganglion cells at variable rates and could eventually leak out into the vitreous humour. Significantly, glutamate levels are elevated in the vitreous humour of glaucoma patients, which supports such a view (55).

The idea of neuroprotection as a future therapy in GON

Any substance will be beneficial in the treatment of GON if it prevents the changes that occur in the optic disc which lead to ganglion cell death and visual field loss. A substance may be thought of as attenuating ganglion cell death by two different pathways: indirectly, as a consequence of lowering IOP, or directly, by interfering with the processes involved in ganglion cell death. The terms “indirect” and “direct” neuroprotection have accordingly been suggested in an attempt to distinguish between the two pathways (11). However, to suggest that both processes qualify as neuroprotection is, in our opinion, potentially confusing. It seems more appropriate to abandon the terms “indirect” and “direct” and simply use the term “neuroprotection in GON” to mean a drug that acts on one or more of the steps which occurs between the initial change in the optic nerve head and the death of the ganglion cells. The implication of this definition is that such a drug must reach the retina in order to be effective (Fig. 2). Moreover, it suggests that a neuroprotectant will be effective in the treatment of all types of glaucoma. Clearly a drug which acts as a neuroprotectant may also lower IOP. It is for these reasons that studies have been conducted in various laboratories over the past few years to determine whether IOP-lowering ophthalmological drugs are potential neuroprotectants.

In experimental studies, many substances have been shown to act as neuroprotectants to attenuate retinal ganglion cell death. Of the drugs presently used to reduce IOP in glaucoma, latanoprost (56), unoprostone (57), brimonidine (58-61) and betaxolol (62, 63) all display neuroprotective properties. However, the evidence

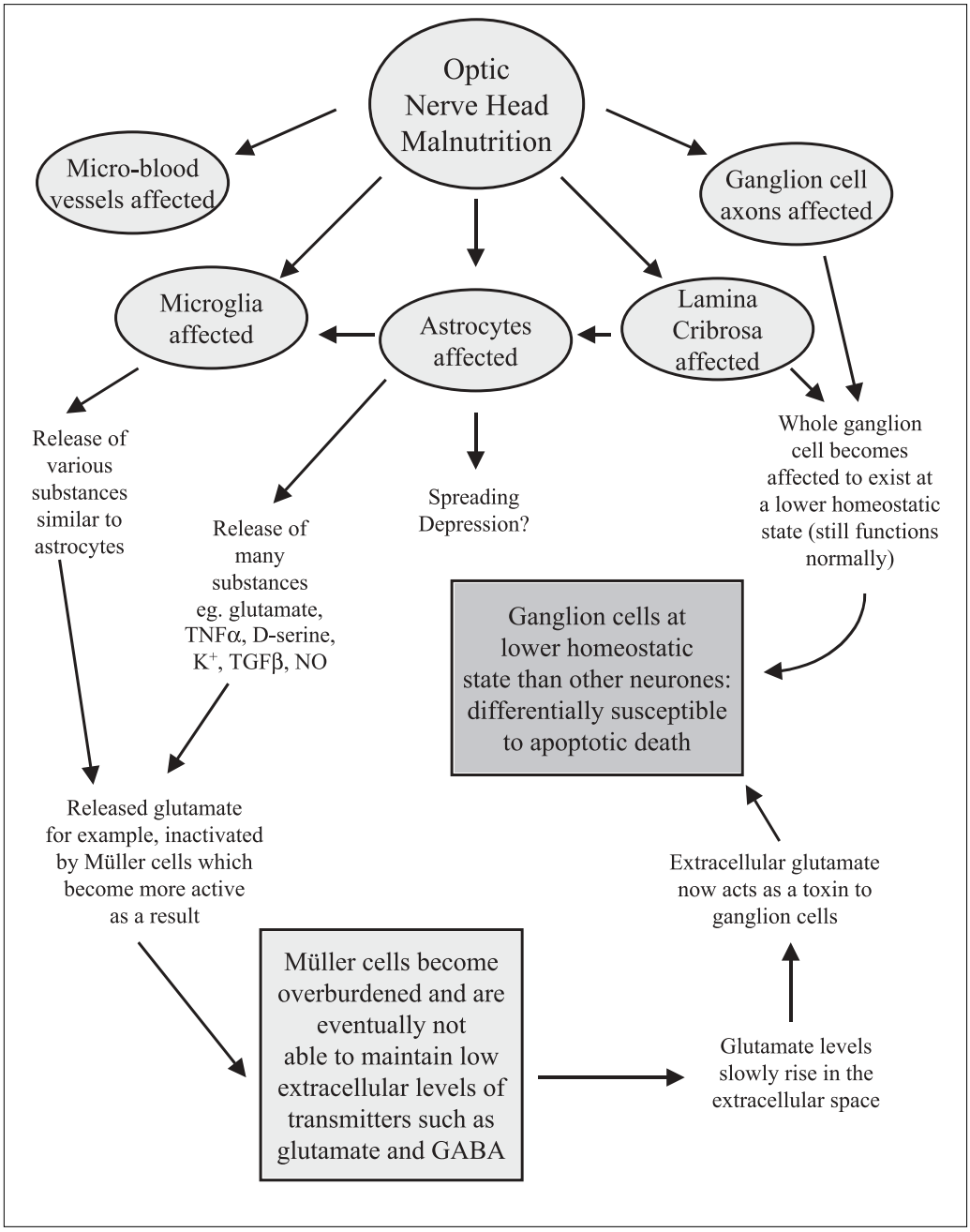

Fig. 2 - *Possible cascade of events leading to ganglion cell death in glaucoma patients after initial insult to the optic nerve head.*

for brimonidine and betaxolol acting in this way is the most impressive. Brimonidine is thought to act as a neuroprotective agent mainly by stimulating the production of basic fibroblast growth factor (bFGF) in the retina. There is good evidence that elevating retinal levels of bFGF can slow down neuronal death (64). Other α_2-adrenoceptor agonists, such as clonidine and apraclonidine, have similar neuroprotective profiles to brimonidine (58,65). Interestingly, the neuroprotective action of betaxolol appears not to be related to its β_1-adrenoceptor blocking activity. Instead, it is thought to act by reducing the influx of calcium and sodium into stressed cells by interacting directly with voltage-gated Na^+ and Ca^{2+} channels (62, 66, 67). Ex-

cessive influx of sodium and calcium into ganglion cells occurs after insults such as ischemia and triggers a cascade of events that leads to cell death. A drug such as betaxolol which can reduce these ion movements will therefore offer neuroprotection. Recent studies have shown other β-blockers have similar properties to betaxolol, although they appear to be less efficacious ion channel blockers and less effective neuroprotectants (68-70).

While β-blockers and α_2-adrenoceptor agonists have been identified as neuroprotectants in animal models of ganglion cell death, definitive data to show that they function in this way in GON patients are lacking. In the case of betaxolol, various independent studies (71-77) have reported that the benefit to visual field was greater in GON patients treated with betaxolol than timolol, despite the fact that the latter is more effective in lowering IOP. Discussion of these studies always centres on the actual accuracy of the measurement of visual field changes, the number of patients studied in each case, and the length of the study. While these studies varied in statistical power to show clinical efficacy, importantly, patients treated with betaxolol tended to do better than patients treated with timolol in all cases. In animal studies, betaxolol appears to be a more efficacious neuroprotectant than timolol (unpublished observations). Such data can be used to support the notion of neuroprotection in GON.

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