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New insights in the pathogenesis and treatment of normal tension glaucoma☆

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Increased intraocular pressure (IOP) is a major risk factor for glaucomatous damage and reducing IOP improves prognosis. Nevertheless, there is little doubt that other risk factors besides IOP such as unstable ocular perfusion are involved. Blood flow is unstable if either the IOP fluctuates at a high level (or blood pressure fluctuates at a low level) or if the autoregulation of blood flow disturbed. A common cause for a disturbed OBF autoregulation is a primary vascular dysregulation (PVD) frequently observed in normal tension glaucoma patients. An unstable blood flow leads to recurrent mild reperfusion injury (chronic oxidative stress) affecting particularly the mitochondria of the optic nerve head. OBF regulation can be improved by magnesium, calcium channel blockers as well as with carbonic anhydrase inhibitors.

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Introduction

A number of questions often arise when dealing with normal tension glaucoma (NTG). Some of the common questions asked are: Why does the therapeutic reduction of intraocular pressure (IOP), although on average improving the prognosis of glaucomatous optic neuropathy (GON), not stop progression in all these patients? [1] Why do we see other patients with GON with an IOP in the normal range? [2••] These observations challenge the pathophysiological concept of glaucoma based solely on IOP. Today, we know that other concomitant factors also play an important role. One important factor is a disturbed ocular blood flow.

On average, blood flow is reduced in glaucoma patients in various tissues of the eye [3,4,5•]. Blood flow reduction is more pronounced in normal tension glaucoma than in high tension glaucoma and comparatively, more in patients with progressive types of glaucoma than those with stable forms of glaucoma [6,7]. Blood flow reduction, however, can also be observed in the nailfold capillaries of the fingers [8], indicating that this reduction is not simply due to an increase in IOP or glaucomatous damage. There is a primary component involved. This primary component, as such, is not arteriosclerosis but rather a primary vascular dysregulation [9].

In this review we aim to give insight into some of the factors, besides IOP, which play an important role in the pathogenesis of GON and briefly describe some of the newer treatment modalities.

Risk factors for glaucoma

Factors associated with an increase of IOP are not the same as factors associated with the development of GON. The risk factors leading to an IOP increase and those leading to GON are described below.

Systemic risk factors for increased IOP

All factors known to be risk factors for artherosclerosis are also risk factors for an increase in IOP (age, smoking, dislipidemia, diabetes mellitus, systemic hypertension, male gender, obesity, etc.). The association between IOP increase and these factors is relatively weak but nevertheless significant [10,11]. Furthemore, treatment of these risk factors (such as physical exercise, weight loss, treatment of dislipidemia, etc.) [12] reduces IOP slightly. It is still a debate why these risk factors are associated with an increase in IOP. On one hand, ischemia can damage the outflow system, in particular the trabecular meshwork (TM), and thereby increase IOP [13]. On the other hand, changes brought about at the molecular level in the TM of glaucoma patients have similarities to changes in the vessel walls of artherosclerotic patients, as for, for example, the expression of ELAM-1 [14]. This signifies that the two pathologies (of the TM and of the arterial wall) may have common causes and similar pathomechanisms.

Systemic risk factors for GON

Elevated IOP is the most commonly identified ocular risk factor in the development of glaucomatous optic neuropathy. It is important to note that not all subjects with elevated intraocular pressure will go on to develop glaucoma (ocular hypertensive subjects) and up to 50% of patients with glaucoma will never have statistically elevated IOP. The correlation between IOP level and

☆ A part of this manuscript has been presented in a lecture by J. Flammer and published in the Internet by Excerpta Media.

progression is very weak [15]. Interestingly, some patients acquire damage before they suffer from an increase in IOP [16]. IOP decreasing therapy on the average improves the prognosis in all types of glaucoma patients. The benefit of IOP lowering treatment, however, is different in the different groups. It is excellent in patients with angle closure glaucoma [17], it is good in primary open-angle-glaucoma (POAG) [12] and relatively modest in NTG patients [18].

Furthermore, there is evidence that systemic arterial hypotension is a relevant risk factor for GON [19,20]. Like an elevated IOP, a low blood pressure does not lead to GON in all subjects. This can be explained by a more or less potent OBF autoregulation [21].

When considering risk factors we have to keep in mind with which kind of patient we are dealing. NTG patients which acquired the damage despite a normal IOP obviously have a very different risk profile, than the so-called 'ocular hypertensives', who when entering a study, have not yet acquired damage despite a high IOP. Risk factors for NTG are female gender [22], race (it occurs more often in Japan than in European or American countries) [23], primary vascular dysregulation (PVD) [24] and low blood pressure [20].

Ocular blood flow (OBF) in glaucoma

Indeed, it is challenging to measure ocular blood flow (OBF)—several methods are used, but there is no gold standard as yet. Nevertheless, OBF can be measured and different instruments are already in daily use, both for clinical and research purposes [4]. Although these different techniques quantify blood flow or blood-flow velocity in different vessels using different methods, the outcomes are very often well correlated.

On average, OBF is reduced in glaucoma patients in various tissues of the eye, including the iris, retina, optic nerve and choroid [3,19,20].

Is the observed reduction in blood flow a primary phenomenon, or is it secondary to other processes? It is obvious that blood flow is reduced in atrophic tissues. A secondary component is therefore involved. Interestingly, however, there are also indications of a primary component. Blood flow reduction can for example, be observed in other parts of the body as well, such as in the nailfold capillaries [21] which cannot be a consequence of glaucomatous damage.

The major cause for this primary component is the PVD syndrome [24], which will be discussed in more detail later.

The role of perfusion pressure

There is still some discussion why OBF is reduced in glaucoma. Some experts focus on perfusion pressure (PP) [25,26], which is traditionally defined as the difference between the arterial BP and the IOP, in the assumption that IOP is equal to the retinal venous pressure.

There is evidence to suggest that low PP, and in particular a fluctuating PP, is a risk factor for the development of GON [2••]. OBF however is not a simple a function of PP. If this would be the case, patients with systemic hypertension would have a better OBF than healthy subjects and treatment of systemic hypertension would reduce OBF. This is normally not the case [27,28]. OBF, like the perfusion of any organ, is the result of the relationship between PP and local resistance to flow. This explains why not all patients with high IOP or low blood pressure have reduced OBF. When treating systemic hypertension we should remember that most drugs reduce blood pressure by reducing peripheral resistance. Therefore OBF, on average, is even improved when blood pressure of patients with systemic hypertension is reduced.

The situation is very different when blood pressure is low in a patient with a PVD. Such subjects not only tend to have low PP but also very often have a defective autoregulation of OBF [21] and may therefore insufficiently adapt to low PP.

But does a reduced OBF indeed lead to GON? Reduction of OBF in animal models, for example by a local application of Endothelin, leads to an atrophic optic nerve head but only mild excavation [29]. OBF is also reduced in conditions other than glaucoma, for example in multiple sclerosis where the marked reduction in OBF is presumed to be due to the high levels of circulating Endothelin [30,31]. These patients, however, either have a normal or pale optic nerve head but do not excavate more often than healthy controls. By contrast, we postulate an unstable fluctuating OBF to lead to glaucomatous damage. An unstable/fluctuating OBF may result from having high and fluctuating IOP, or normal but fluctuating IOP occurring in subjects with disordered vascular autoregulation (PVD).

The role of retinal venous pressure

In normal circumstances the retinal venous pressure is approximately equal to the intraocular pressure, explaining the physiological phenomenon of spontaneous venous pulsation. In glaucoma patients, the retinal venous pressure is often increased [32,33,34••] and based on our clinical experience it is particularly increased in those patients with a PVD. The fact that the retinal venous pressure is increased in glaucoma patients indicates that the perfusion pressure is lower than one would calculate, based on blood pressure and IOP.

Measurements of retinal venous pressure (RVP) are done by means of an ophthalmodynamometer [34••]. Simply stated, a contact lens dynamometer, is placed onto the eyeball in the same way as the conventional three-mirror

lens after instillation of local anaesthesia. The force necessary to induce a venous pulsation – so called ophthalmodynamometric force (ODF) – is recorded. RVP is calculated as the summation of the ODF with the IOP.

Vascular dysregulation syndrome

Subjects with a PVD syndrome have an inborn tendency to respond differently to various stimuli such as cold [35]. Among the most apparent pathological reactions are the vasoconstrictions. But why do these subjects constrict their vessels more than others?

Subjects with a PVD have a normal capacity to produce ATP. Under certain circumstances, however, where these subjects do not use as much ATP, such as when they sit quietly in a cold environment, they are not able to produce as much heat as others. This is one of the reasons why these subjects constrict the vessels in their extremities: to reduce heat loss. Interestingly, as they constrict the vessels in their skin they also constrict their ocular vessels [36].

The PVD syndrome occurs more frequently in females than in males [37], in Japanese than in Caucasians [38,39], and in academics than in blue collar workers [40] as has been observed in Raynaud's phenomenon. The symptoms normally first manifest during puberty and mitigate with aging.

Unfortunately there is no gold standard in diagnosing a PVD. However, there are a number of signs and symptoms that point towards a PVD. Subjects with a PVD often have cold extremities like cold hands or feet [41], they tend to have normal or low body mass indices [35], the feeling of thirst is often reduced (they drink because they know they have to drink and not so much because they are thirsty) [42], they tend to have low blood pressure especially when they are young [43], they more often suffer from migraines than non-PVD subjects (although PVD and migraine are two distinct entities) [44]. PVD subjects have often an altered drug sensitivity due to differential expression of ATP-Binding Cassette (ABC) transporter proteins [45]. PVD subjects have a better smell perception than non-PVD subjects [46,47]. They have, on average, a longer sleep onset time [48], especially when they are cold. Based on our clinical experience they often have a meticulous personality and are often successful in their professions [49].

The regulation of OBF in patients with PVD is different. In terms of circulation, their retinal vessels show a higher spatial irregularity and are stiffer, and vasodilation to flickering light is reduced [50,51]

In a provocation with hand-grip test (a stimulation of the sympathetic nervous system) their choroidal vessels constrict more than normals [52]. Vessels in vasospastic subjects conduct pulse waves faster and are thus stiffer than those in nonvasospastic subjects [53].

Dysfunction of regulation leads to an unstable ocular perfusion especially when IOP or blood pressure fluctuates. The resulting instability of blood flow leads to a repeated, but very mild, reperfusion contributing via oxidative stress to glaucomatous damage. These phenomena probably contribute to the development of glaucomatous damage and are discussed in the following section.

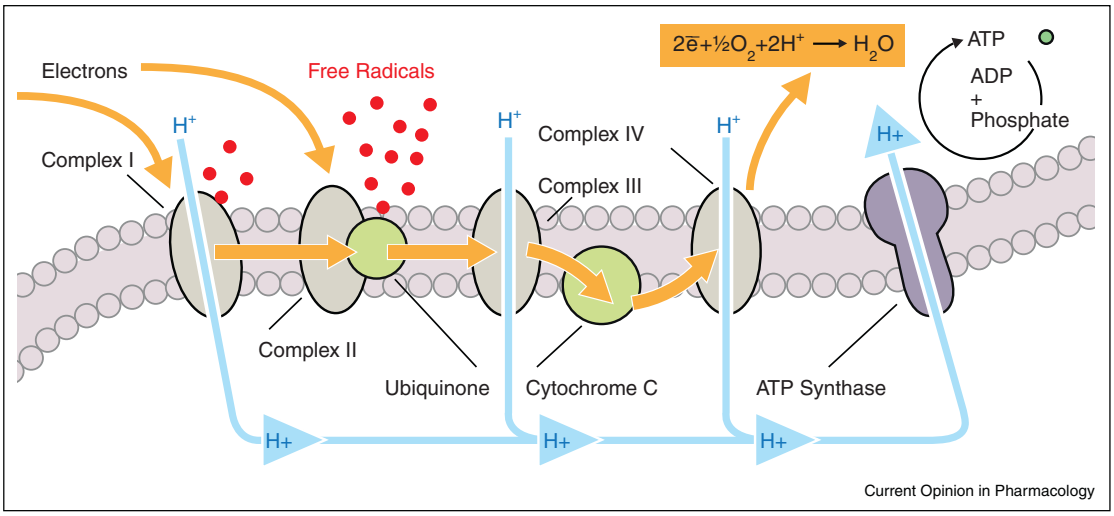
The role of oxidative stress

Oxidative stress is induced by an unstable oxygen supply (reperfusion injury) [54,55]. In POAG, oxygen tension in the tissue often falls temporarily. This drop is very mild but recurrent so that there is a long-term cumulative effect of the small amount of damage caused by these reductions in oxygen tension. To some extent, such a reduction in oxygen tension leads to an adaptation which is called preconditioning. This results in cells becoming resistant to further reductions in oxygen tension. Reperfusion damage is induced when tissue oxygen tension is reduced beyond a threshold limit for that tissue. Tissue infarction occurs when the reduction in oxygen tension is of a greater magnitude or if it is sustained. When the oxygen drop is even larger or lasts longer tissue infarction results. This occurs rarely in glaucoma but more commonly as a consequence of other diseases

Reperfusion occurs both in patients with either high IOP or very low blood pressure exceeding the capacity of autoregulation. It also occurs in patients with a normal (or a mildly increased) IOP or a normal (or mildly decreased) blood pressure if subjects suffer from disturbed autoregulation. This recurrent mild reperfusion leads to a chronic oxidative stress, especially in the mitochondria (Figure 1)

There is evidence to suggest that oxidative stress plays an important role in the pathogenesis of GON. Analysis of DNA breaks by means of comet assay in the circulating lymphocytes revealed an increase in DNA breaks in glaucoma patients compared to age-matched controls [56]. Oxidative stress is known to result in an increase in Endothelin-1 (ET-1); various studies have demonstrated an increase in ET-1 in glaucoma patients, particularly those progressing despite a 'normalized' IOP [57,58•]. Metalloproteinases (MMP-2 and MMP-9) are upregulated in the optic nerve heads of glaucoma patients. There is an upregulation of MMP-9 even in circulating lymphocytes [59]. Oxidative stress damages a variety of molecules including proteins. Unlike damaged DNA, damaged proteins cannot be repaired. Nature has developed sophisticated methods to eliminate damaged intracellular proteins. These proteins are first marked by

Figure 1



Formation of free radicals in the mitochondria. Under normal circumstances, the electrons travel down from one complex to another until they are finally accepted in pairs by the oxygen molecule. If, however, oxygen concentration, is reduced, the electrons congest and electron flow is impaired. As soon as the oxygen concentration normalizes, some of these electrons go astray and react with nearby oxygen molecules to form free radicals. Based on: J. Flammer, M. Mozaffarieh and H. Bebie. Basic Sciences in Ophthalmology. Physics and Chemistry. Springer.

ubiquitin and then pulled electrostatically into the proteosomes where they are cut in pieces which are then recycled. The activity of the proteosomes therefore gives us an indirect measure of proteins damaged. Indeed, the expression of 20S proteosome alpha subunit is upregulated in glaucoma, further supporting the hypothesis that oxidative stress contributes to the development of glaucomatous damage [60].

As explained above this mild reperfusion leads to chronic oxidative stress which specifically affects the mitochondria. There is a high density of mitochondria in the optic nerve head due to high energy demands, which is a consequence of the lack of myelin in that area. Oxidative stress leads to increasing damage to the mitochondria and this results in increasingly less efficient energy supply to the optic nerve head. Other cellular components are affected by oxidative stress and undergo a process equivalent to accelerated aging. In parallel, activated astrocytes respond dynamically to change the microenvironment. These processes combined induce a pathogenetic state which will be discussed in the next section [61].

The pathogenetic concept

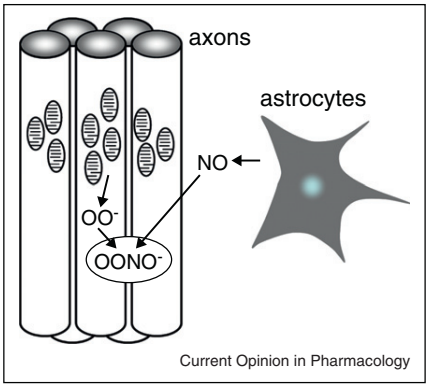
There are two main pathogenetic components: first, the activation of the astrocytes and second, damage to the axons (graphical abstract).

Mechanical stress (e.g. by an increase in IOP) activates astrocytes by stimulating the epidermal growth factor receptor (EGFR) [62]. Astrocytes, however, are also activated by Endothelin [63], which is upregulated as a consequence of cell stress as for example due to reperfusion injury (RI) [54].

The activation of the astrocytes alters the local microenvironment in the optic nerve head and its surroundings. This includes also a high level of Endothelin which not only can further reduce OBF but also interferes with axonal transport [64]. The upregulation of nitric oxide synthase-2 (NOS-2) leads to an increase in NO concentration. NO is a small, easily diffusible, free radical with a very short half-life whose effect is usually limited to neighboring cells. NO itself is not damaging but when NO reaches retinal ganglion cell axons, where there is a high concentration of superoxide radicals (O_2^-) caused by reperfusion injury, this may lead to the formation of peroxynitrite (ONOO−) [65]. Both superoxide and peroxynitrite contained within the axons can diffuse along the axons both towards the retina and towards the lateral geniculate nucleus inducing apoptosis of neural cells (Figure 2). The fact that nitrosylation of SH-groups is observed even in the lateral geniculate nucleus suggests that peroxynitrite plays a role in glaucoma pathogenesis [66].

In parallel to the loss of retinal ganglion cells and their axons, tissue remodeling takes place, which is not only a consequence of mechanical forces, but also of an active biological process including the effect of MMPs. MMP upregulation results in increased degradation of extracellular matrix which is remodeled in an altered fashion, both chemically and morphologically. Alternatively, astrocyte and MMP remodeling of ECM can result from

Figure 2



Formation of peroxynitrite. The reaction between the superoxide anion ($O_2^{\bullet -}$) produced by the mitochondria located numerously in the axons of the optic nerve head and nitric oxide ($NO^{\bullet}$) produces the highly damaging peroxynitrite ($ONOO^-$). Peroxynitrite ($ONOO^-$) can diffuse within the axons both into the direction of the lateral ganglion geniculate nucleus and towards the retina inducing damage on both sides. Reproduced with permission from Neufeld AH. Surv Ophthalmol 1999;43:S129–35.

the processes defined within the biomechanical theory of glaucoma [67•]

Endothelin and MMP-9, which are both increased in the circulation, may diffuse from the choroid into the ONH in glaucoma, leading to vasoconstriction and breakdown of the blood–brain barrier. This sequence of events may explain the incidence of splinter hemorrhages seen with increased frequency in NTG [68].

Novel therapeutic strategies may be formulated if each of these pathophysiological components is better understood; such strategies are discussed in the next section.

Therapeutic consequences

It is well known that an IOP reduction improves, on average, the prognosis of all types of glaucoma. It is also known, however, that patients may continue to progress despite achieving their optimal 'target' IOP. This insight has lead to the need to develop new therapeutical approaches [69–71]. Some of these approaches are already in (limited) clinical use, whereas others are still being investigated experimentally. For the purposes of this review, we will focus on treatments that are already in clinical use.

Low blood pressure increases the probability of visual field deterioration in glaucoma patients. Blood pressure should be modified to prevent nocturnal dipping [72].

Vascular regulation can be improved locally by carbonic anhydrase inhibitors and systemically with magnesium [73] or low dose calcium channel blockers [74•,75]. Oxidative stress at the level of mitochondria can be reduced by gingko biloba [76–78,79•].

Conclusions

Glaucoma is a disease, for which diagnosis and treatment is not solely associated with elevated IOP. Today, the concept of glaucoma implies that this is a multifactorial disease and although elevated IOP still remains an important risk factor, glaucomatous damage results from a combination of elevated IOP and IOP-independent risk factors. Throughout the past century medical, laser and surgical treatments have focused on methods of lowering IOP. However, despite successful lowering of IOP, many patients continue to have progressive damage whereas others acquire damage at normal or even unphysiologically low IOP levels, implying the presence of non-IOP dependent factors.

Two areas of non-IOP dependent risk factors that are regarded as major risk factors are disturbed ocular blood flow and oxidative stress, which can both be diagnosed and treated. The elucidation of these and other IOP-independent risk factors bring about a new therapeutic era challenging the conventional target in glaucoma therapy.

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