EXPERT REVIEWS

Calcium channel blockers: their use in normal tension glaucoma

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The treatment of normal tension glaucoma can be difficult. Some normal tension glaucoma patients show progression of glaucomatous optic neuropathy despite an intraocular pressure in the normal range, and sometimes even with an intraocular pressure in the low teens. The question therefore arises as to whether there are other therapeutic options besides lowering the intraocular pressure. One treatment modality discussed in the literature is calcium channel blockers. We suspect that calcium channel blockers are particularly useful in glaucoma patients having a primary vascular dysregulation.

Keywords: autoregulation • calcium channel blockers • glaucomatous optic neuropathy • ocular blood flow • primary vascular dysregulation

Primary vascular dysregulation

Owing to the complex challenge posed in the successful treatment of normal tension glaucoma (NTG) [1], new therapeutic options besides simply lowering the intraocular pressure (IOP) must be investigated [2]. The demand for blood flow to different organs can vary quite rapidly from one moment to the next – this explains why a sophisticated local regulation of blood flow is necessary. Dysregulation simply means that blood flow is not properly adapted to the particular need for that moment. Dysregulative mechanisms can therefore lead to an over- or underperfusion, a condition that is usually temporary. While a short over- or underperfusion induces no or only insignificant damage, damage provoked by repeated underperfusion can add up over a prolonged period of time. An underperfusion occurs when a vessel overconstricts in response to a stimulus: this condition is known as a vasospasm [3]. In patients suffering from vasospasms, one often sees that other vessels either do not dilate when needed or they dilate too much. Because it is not only the one incident that is involved, the term 'vasospasm', or 'vasospastic syndrome' (if more than one organ is involved) has been replaced with the more global term, 'vascular dysregulation' [4]. There are a number of causes that lead to local or systemic vascular dysregulation.

We differentiate between a primary vascular dysregulation (PVD) and a secondary vascular dysregulation (SVD) [3]. While PVD is an inborn predisposition to respond differently to various stimuli, a SVD is a local or systemic dysregulation as a consequence of an underlying disease. A number of diseases, including autoimmune diseases such as multiple sclerosis [5,6] or rheumatoid arthritis [7], lead to a marked increase of circulating endothelin-1 (ET-1). In these diseases, cells other than endothelial cells start producing ET-1, which, in turn, reduces ocular blood flow (OBF). Although increased levels of ET-1 reduce OBF, they do not significantly interfere with autoregulation. Therefore, while SVD reduces baseline OBF without exerting a major impact on autoregulation [8], PVD only mildly influences baseline OBF but exerts a major impact on autoregulation (Figure 1). Accordingly, fluctuating perfusion pressure leads to a fluctuation in the OBF of patients with PVD, but less so in patients with SVD. Therefore, the consequence of SVD is a more-or-less constant OBF reduction (with a certain risk for optic nerve head [ONH] atrophy, but not for glaucomatous optic neuropathy [GON]), whereas the consequence of PVD is rather an unstable blood flow. Unstable blood flow leads to an unstable oxygen supply, and this in turn increases oxidative stress. Oxidative stress, particularly in the mitochondria, is involved in the

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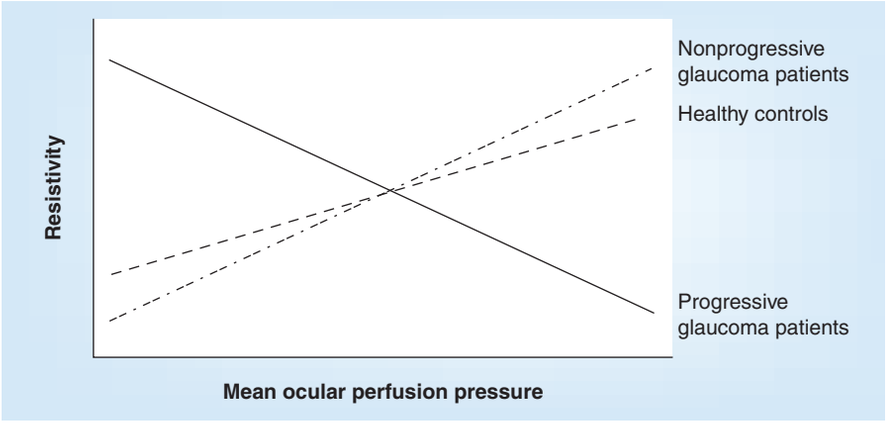

Figure 1. Autoregulation of ocular perfusion. As mean ocular perfusion drops, the resistance to flow is reduced in healthy subjects in order to keep flow constant (autoregulation). Whereas patients with nonprogressive glaucoma respond, as do healthy controls, patients with progressive glaucoma show a disturbed autoregulation despite a normal intraocular pressure.
Reproduced with permission from [103].

pathogenesis of GON, and explains the relationship between PVD and GON [3]. Because there are many signs and symptoms that point to PVD – some of which are described later – subjects with this condition are easily recognizable.

Signs & symptoms of PVD

General symptoms of PVD

Primary vascular dysregulation subjects show certain signs and symptoms more often than non-PVD individuals, and the more signs and/or symptoms present, the greater the likelihood of PVD. Dysregulation can be more or less prominent, which is why the symptoms are more pronounced in some people and less in others. The syndrome is observed more often in females than in males; in slim than in obese individuals; in academics than in blue collar workers; and in Asians than in Caucasians [9]. The symptoms also depend on the person's age. Most of the symptoms manifest themselves for the first time in puberty and mitigate with age. After menopause, these symptoms generally attenuate or may even completely disappear.

The leading symptom in PVD is cold extremities [3] and their feeling of thirst is also reduced [10]. PVD subjects usually have colder feet, explaining why they need longer to warm them up. They additionally have a prolonged sleep onset time owing to the fact that there is a strong correlation between foot temperature and sleep onset [11]. PVD subjects also have altered drug sensitivity. This is partially due to an altered gene expression of the ATP-binding cassette transport proteins [12]. PVD subjects often also have a low blood pressure when they are young and particularly at night. Moreover, their ET-1 levels in their circulating blood are slightly increased, and in contrast to non-PVD subjects, their ET-1 sensitivity is inversely related to blood pressure [13].

PVD & eye diseases

Besides glaucoma, PVD is also a risk factor for various other eye diseases. It is rarely the only cause of such diseases, yet it increases their risk. Some of these are briefly discussed here.

Anterior ischemic optic neuropathy (AION) normally occurs in elderly patients with risk factors for atherosclerosis. It is occasionally observed in younger patients without any risk factors for atherosclerosis. These younger patients normally suffer from a PVD [3] and the AION is provoked by major emotional stress.

Retinal vein occlusion (RVO) occurs more often in elderly subjects and, interestingly, besides increased IOP, risk factors for atherosclerosis are also risk factors for RVO. Occasionally, an RVO occurs without any recognizable risk factors for atherosclerosis. These individuals often suffer from a PVD [14].

Susac syndrome is defined as a circulatory disturbance in the eye, the ear and the brain. It is often assumed that this might be a consequence of an inflammatory process. We have made the observation that these subjects often suffer from a PVD [15].

Central serous chorioretinopathy is a reversible local disturbance of the outer retinal blood–brain barrier [16] accompanied by a dysregulation of the adjacent choroidal circulation [17]. Based on our clinical experience, patients with a central serous chorioretinopathy often suffer from a PVD syndrome.

PVD & eye circulation

Baseline blood flow is often reduced in PVD subjects. In certain patients, however, blood flow is normal under baseline conditions but disturbed when challenged. Provocation tests are therefore useful when measuring blood flow as they provide other and more relevant information. Angiography [18], visual evoked potentials [19–21], color Doppler imaging [22] or even perimetry [23] have been performed under artificially increased IOP. Visual fields were tested before and after cold provocation [24] or the application of drugs, such as calcium channel blockers (CCBs) or carbonic anhydrase inhibitors [25], or after breathing carbon dioxide (CO_2) [26]. Exposing the retina to flickering light causes a widening of retinal vessels, a phenomenon called neurovascular coupling [27].

The regulation of OBF in patients with PVD is different in a number of ways: the retinal vessels demonstrate a high level of spatial irregularity [28] and are stiffer [29]. When stimulated by flickering light, the retinal vessels of PVD subjects respond with a smaller vasodilation than those of normal subjects; that is, the neurovascular coupling [30] is suppressed [31]. During provocation with the hand-grip test, the choroidal vessels in the retina constrict more than normal [32]. In contrast to non-PVD subjects, the OBF of PVD patients correlates with peripheral blood flow [33]. The circulation in their eyes is related to perfusion pressure; in other words, autoregulation is disturbed [34]. This disturbed autoregulation explains the risk for glaucomatous damage. A similar disturbance of autoregulation can be observed in glaucoma patients, which progresses despite a normal or normalized IOP [35]. For this reason, we will briefly discuss what is meant by autoregulation.

Autoregulation

Autoregulation is the component of local regulation that compensates for alterations in perfusion pressure [8]. If, for example, the perfusion pressure is decreased (e.g., by a decrease in the blood pressure), blood flow initially falls then returns to normal levels after a short time. Perfusion pressure, in turn, is defined as the difference between arterial and venous pressure [36]. In the eye, venous pressure is equal to or slightly higher than IOP. When autoregulation works properly, there are no changes in retinal and optic disc perfusion when either the IOP or the blood pressure fluctuates within a certain range.

Glaucomatous optic neuropathy

Glaucomatous optic neuropathy is characterized by a loss of retinal ganglion cells and their axons together with major tissue remodeling, leading to optic nerve excavation. Crucial in the pathogenesis is the activation of glial cells, especially astrocytes, which, in turn, alters the microenvironment in the ONH.

There is evidence that it is not so much the constant blood flow reduction that causes GON, but rather unstable OBF [4,37]. OBF is unstable if either the IOP fluctuates at a high level, or if autoregulation is disturbed. As previously mentioned, the main cause of disturbed autoregulation is a PVD syndrome.

The assumption that PVD plays a role in GON explains why systemic hypotension in these subjects is a risk factor (because they cannot compensate with appropriate autoregulation), why females more often suffer from NTG than males (females suffer more often from PVD) [38], why NTG occurs more often in the Japanese than in Caucasians (Japanese suffer more often from PVD) but also why NTG patients, and particularly why females, more often have splinter hemorrhages (because PVD in itself is a risk factor for ONH hemorrhages) [39,40].

Rationale for the use of calcium channel blockers

The role of calcium

Calcium plays a role in both physiological and pathological processes. In smooth muscle cells, intracellular calcium concentration is partly regulated by ET-1 (Figure 2). Under physiological conditions, the majority of ET-1 is produced by the vascular endothelial cells. ET-1 is secreted predominantly abluminally but a small portion is secreted intraluminally, thereby leading to a certain concentration of ET-1 in the blood. While a slight increase in the ET-1 level points to PVD [14,41,42], a higher level points to SVD [5,7]. ET-1 levels have been described as being high in NTG patients [43]. ET-1 leads to a vasoconstriction of extraocular vessels [44,45], reduces ONH blood flow [46], impairs anterograde and retrograde axoplasmatic transport [47,48], and activates astrocytes [49].

Since ET-1 may be involved in the pathogenesis of glaucomatous damage, ET-1 blockers are of interest [50]. Although ET-1 blockers are used for experimental work, they are not yet clinically available for use in glaucoma. We know, however, that CCBs, such as nifedipine, inhibit contractions to ET-1 in the porcine ciliary arteries, while endothelium-dependent relaxation to bradykinin as well as endothelium-independent relaxation to sodium nitroprusside remains unaffected [51]. By acting on vascular smooth muscle, CCBs can lead to vasodilation or relief from vasospasm [52,53], and can partially block the effect of ET-1 [54]. Thus, while we are waiting for ET-1 blockers to become clinically approved for the treatment of vascular dysregulation, in selected cases CCBs can already be implemented.

Types of CCBs & their site of action

Calcium channel blockers are a chemically and pharmacologically diverse group of drugs that reduce the calcium conduction of calcium channels. CCBs are generally classified into three groups according to their chemical structure: dihydropyridines (e.g., nifedipine), phenylalkylamines (e.g., verapamil) and benzothiazepines (e.g., diltiazem) [55]. The selectivity of these CCBs for the heart and smooth muscle cells varies. Dihydropyridines have a greater selectivity for vascular smooth muscle [56] than for myocardium because they block smooth muscle calcium channels at concentrations below those required for significant cardiac effects. Benzothiazepines and phenylalkylamines show less selective vasodilator activity than do dihydropyridines and exert a direct effect on the myocardium [57].

The main portals of entry for calcium into cells are voltage-gated calcium channels that open when the cell membrane is depolarized, and sodium–calcium exchange. In addition, there seem to be receptor-operated calcium channels (ROCs) [58], which open in response to receptor ligands, such as noradrenaline acting on α-1 adrenoreceptors. Neither ROCs nor the

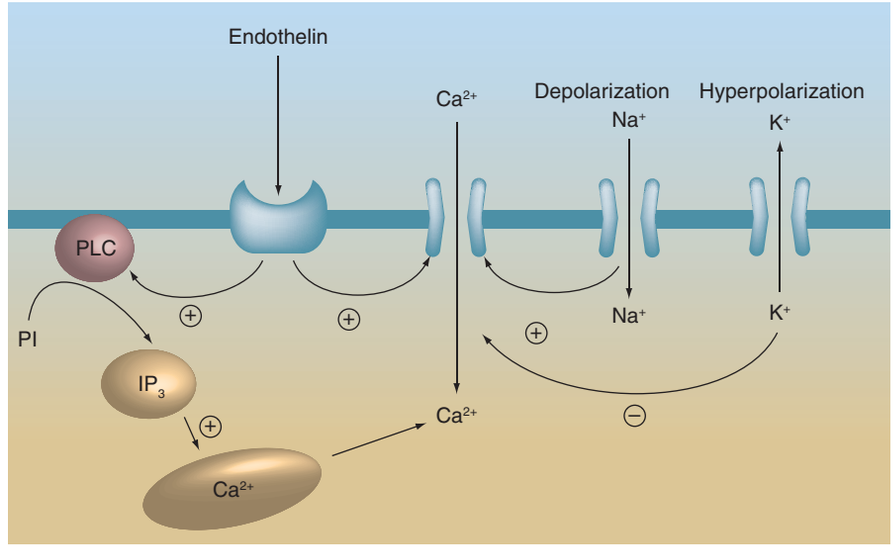

Figure 2. Stimulation of endothelin receptors. Endothelin, similar to angiotensin-2 and α-agonists, leads to an increase in the intracellular calcium, both by opening the calcium channels and by liberation from internal storage sites.

sodium–calcium exchange carriers appear to be targets for any of the known types of CCBs, which act on voltage-gated channels [59].

There are three distinct types of voltage-gated calcium channels: L, N and T [60,61]. They are distinguishable on the basis of their various properties, such as the voltage range over which they open, their tendency to close, and so on. The physiological functions of these channels are, at present, only partially understood. However, it is believed that the channel responsible for calcium entry that triggers neurotransmitter release is the N channel [62], and that the main channel occurring in smooth muscle is the L channel [63].

The effects of CCBs are well documented both in studies on OBF and visual fields.

Studies on the effect of CCBs on OBF

Ex vivo studies show that CCBs reduce the vasoconstrictive effect of ET-1 [51,64]. Various animal studies show that OBF, particularly ONH blood flow [65], is increased after the application of CCBs such as nicardipin [66,67]. CCBs mitigate the OBF-reducing effect of an ET-1 infusion in healthy volunteers [54]. Studies on healthy subjects with PVD show that CCBs improve PVD syndrome [68]. Studies on glaucoma patients also show an improvement in OBF [69–71].

Studies on CCBs & visual fields

Perimetry can indirectly provide information about OBF. Perimetry is used to assess the differential light sensitivity (DLS). The outcome fluctuates in normal eyes and this fluctuation is amplified in glaucoma patients. The fluctuation has both a short- and a long-term component [72]. The short-term component depends on factors such as damage to the visual field or cooperation of the patient [73], while the long-term component seems to be influenced by ocular circulation, among other factors. In one experimental study in healthy volunteers, Brandl *et al.* demonstrated that DLS strongly correlates with the blood oxygen saturation [74].

Studies that distinguish between PVD and non-PVD found a positive effect of CCBs on visual fields in PVD patients. Short-term studies indicate that treatment with CCBs improve visual fields in PVD patients (both those with and without glaucoma) (Figure 3) [52,75–77]. The same effect can be achieved by CO_2 inhalation or by carbonic anhydrase inhibitors, thereby indicating that these short-term visual function improvements are also most probably due to vasodilation [78]. Therefore, a relatively quick (reversible) change in the visual field can be an indirect sign of a change in oxygen supply.

The long-term improvement in visual fields after treatment with CCBs has only been observed in those patients who responded to CCBs [52] or to CO_2 breathing [26] with an improvement in the visual fields in the short term. Although the term 'PVD' was not used in this particular study, these were typical PVD patients [77].

Other researchers have not distinguished between PVD and non-PVD subjects in their studies on visual field effects after treatment with CCBs: Netland *et al.* found that, when compared with controls, NTG patients taking CCBs showed no evidence of progressive optic nerve damage [79]. Harris *et al.* found an improvement in visual function only in those with improved indices of retrobulbar perfusion [80].

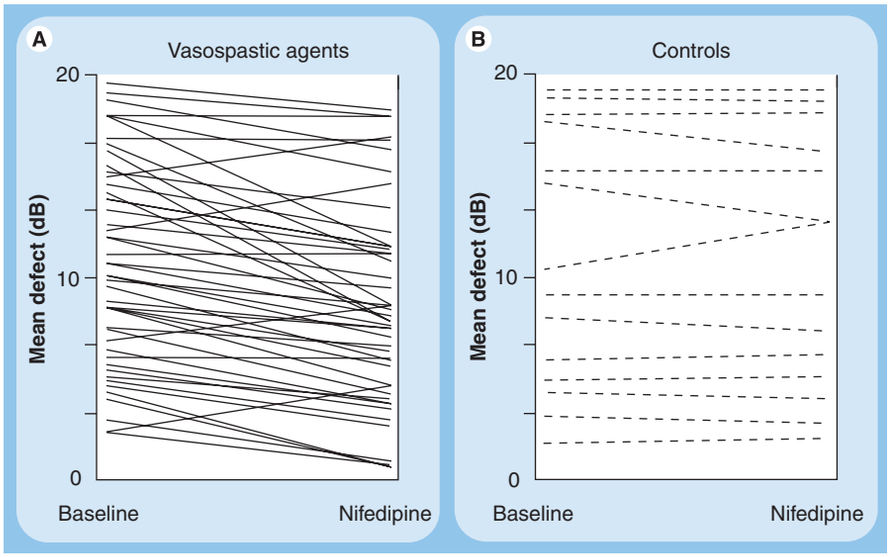

Figure 3. Short-term effect of nifedipine. Mean defect of visual field test (Octopus program G1) at baseline and 60 min after intake of 20 mg sustained-release nifedipine in: **(A)** improvement in patients with a primary vascular dysregulation (PVD), and **(B)** no change in patients without PVD. Note that the smaller the mean defect, the better the visual function. The improvement in mean defect in subjects with a PVD was statistically significant ($p = 0.0001$), and the effect of the treatment was significantly larger for those with a PVD than those without a PVD ($p = 0.017$). When treatment was continued for 12 months, the improvement in the group with vasospasm was still detectable (not shown here).
Reproduced from [52].

Studies on CCBs & contrast sensitivity

A significant increase in contrast sensitivity was observed after treatment with CCBs in both healthy subjects [81,82] as well as in NTG patients [80,82].

Advice to clinicians

Which drug to use?

This question cannot be definitively answered as, to date, there are no studies that compare the effects of CCBs with each other in this particular respect. Although some physicians prefer to use liposoluble CCBs (so-called centrally acting CCBs), in theory water-soluble CCBs (e.g., nifedipine) ought to be just as effective as they can easily diffuse from the choroid into the ONH.

CCBs & blood pressure

The blood pressure-lowering effect of CCBs are well-documented in the literature [83–86]. As low blood pressure is a risk factor for glaucomatous damage and PVD, patients often suffer from arterial hypotension, and consequently some physicians are wary of prescribing CCBs. From our point of view, this effect is a minor problem for the following reasons:

Our past clinical experience has shown that, in contrast to patients with hypertension, individuals with hypotension do not normally show a further blood pressure reduction with CCBs.

We recommend the use of low doses of CCBs for the following reasons:

- Even a low dose (5 mg) of nifedipine inhibits the ET-1-induced reduction of OBF [54]. Moreover, low-dose CCBs have been shown to improve ocular hemodynamics without affecting blood pressure significantly in both healthy subjects [87] as well as in glaucoma patients [71,88–90];
- We do not wish to lower the blood pressure any further;
- Even if blood pressure is lowered after the application of CCBs, the ONH blood flow still increases [91].

Magnesium: an alternative to CCBs

Magnesium has been shown to have calcium-antagonistic-like properties [92] and to inhibit calcium influx through voltage-operated calcium channels [93]. In precontracted vessels, magnesium causes vasorelaxation (Figure 4). In addition, contractions to various agonists were shown to be attenuated in the presence of high concentrations of magnesium [94–96]. In addition to inhibiting calcium influx, magnesium also inhibits intracellular calcium release from storage sites [97]. Magnesium acts principally in the same way as do CCBs [98]. However, it has a weaker effect, shows fewer side effects and may therefore be a safe alternative [99,100].

Patient selection

Obviously, not all glaucoma patients will benefit from CCB treatment, but it does appear advantageous to those glaucoma patients who have a PVD [3,36]. It is therefore necessary to recognize the PVD syndrome in glaucoma patients [9] so that the right patient is treated with the right drug.

Conclusion

An unstable OBF contributes to the pathogenesis of GON [36]. OBF is unstable if either IOP fluctuates at a high level (or blood pressure at a low level), or if autoregulation is disturbed. The main cause of disturbed autoregulation is PVD syndrome [34]. To date, no Phase III study meeting internationally accepted criteria exists that proves that CCBs are effective in PVD. However, various studies on OBF, visual fields and contrast sensitivity indicate that the use of CCBs might indeed be beneficial. Other non-IOP-lowering treatments have been summarized elsewhere [101,102].

Expert commentary

The goal of glaucoma treatment is the preservation of visual function. In high-tension glaucoma, this is mainly achieved by reducing IOP. The effect of IOP-lowering treatment is less effective and less well documented in patients with NTG. Although IOP may play a role in this group of patients, other risk factors are obviously also involved. Knowledge about the effects of modulating other risk factors is still limited. We know, however, that oxidative stress due to an unstable blood flow plays a role in the pathogenesis of damage. OBF is particularly unstable in patients with PVD. Among the drugs currently available, CCBs are considered the most promising treatment for regulating OBF.

Indeed, treatment with CCBs, especially when used at low doses, has repeatedly been reported to be beneficial for NTG patients, particularly when they suffer from PVD. These patients normally present both an irreversible as well as a reversible component of visual field defects. If the visual fields improve after short-term treatment with certain drugs (i.e., the reversible component decreases), then there is a high probability that this treatment will also be beneficial when used long term.

Magnesium is a physiological CCB. While its effect is weaker, side effects are also less pronounced than those of CCBs. It is therefore advisable to begin treatment with magnesium and then to switch over to CCBs only if the effect of magnesium is insufficient. Nevertheless, it can be difficult to find an appropriate CCB at the right concentration. As the main indication for CCB

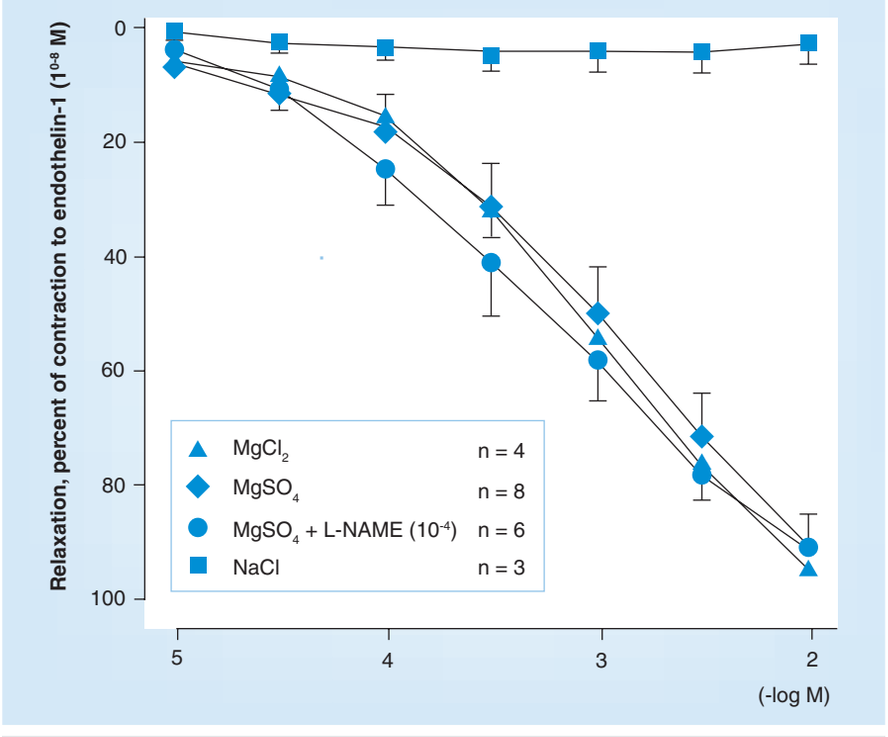

Figure 4. Magnesium inhibits the effect of endothelin-1. The relaxing effect of increasing concentrations of $MgSO_4$ and $MgCl_2$ added to endothelin-1-precontracted porcine ciliary arteries (-10^{-8} M) is shown. NaCl, which has the same osmolarity as $MgSO_4$, did not evoke a relaxation.
Reproduced from [98].

administration is the treatment of systemic hypertension, low-dose CCBs are usually not available. As an exception, nifedipine is available in a liquid form, which can be applied as low-dose drops.

Five-year view

Intraocular pressure-lowering treatment will continue to be very important. It is possible, but from our current standpoint rather unlikely, that better IOP-lowering drugs will come onto the market. The increasing awareness of risk factors other than IOP will continue to stimulate research for alternative treatments. There are two major promising approaches:

- Avenues to improve the regulation of blood flow are likely, as it is well known that disturbed regulation of blood flow plays a crucial role in the pathogenesis of glaucoma. CCBs may be adapted for this use and, in particular, endothelin blockers show great promise;
- Oxidative stress in the mitochondria, particularly in the axons of the optic nerve head of glaucoma patients, also plays a role in the pathogenesis. Efficient antioxidants reaching these areas are now being developed and tested. In addition to antioxidative nutrition, phytotherapeutics, such as ginkgo, show great promise.

Financial & competing interests disclosure

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Key issues

- Intraocular pressure – although an important risk factor – is not the only risk factor for glaucomatous optic neuropathy.
- The impact of ocular blood flow for glaucomatous optic neuropathy has been clearly established.
- We differentiate between a primary vascular dysregulation (PVD) and a secondary vascular dysregulation. While PVD is a congenital predisposition to respond differently to various stimuli, a secondary vascular dysregulation is a local or systemic dysregulation as a consequence of an underlying disease.
- Various studies show that calcium channel blockers (CCBs) improve ocular blood flow, visual fields and contrast sensitivity.
- Not all glaucoma patients profit from treatment with CCBs. Only those with a PVD benefit from treatment.
- We recommend the use of low doses of CCBs for normal tension glaucoma patients with a PVD.
- Magnesium acts principally in the same way as CCBs. However, it has a weaker effect and may therefore be a safe alternative.

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