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Is the medication used to achieve the target intraocular pressure in glaucoma therapy of relevance? – An exemplary analysis on the basis of two beta-blockers

Matthias C. Grieshaber*, Josef Flammer

Department of Ophthalmology, University Hospital of Basel, Basel, Switzerland

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A B S T R A C T

Glaucoma, the most common optic neuropathy (GON) is characterised by the loss of retinal ganglion cells and their axons, as well as tissue remodelling of both the retina and the optic nerve head with corresponding visual field defects. Elevated intraocular pressure (IOP) is generally regarded as the major risk factor for glaucoma and its reduction is the most common target for therapy of GON. There are indications that the greater the IOP reduction, the better is the visual field prognosis. This article investigates, on the basis of two beta-blockers, betaxolol and timolol, whether the amount of IOP reduction is truly a good surrogate for successful glaucoma therapy with respect to visual field outcome.

Contrary to what is generally expected, our analysis of the literature exemplifies that despite a smaller IOP reduction, patients treated with betaxolol had a smaller rate of visual field deterioration than patients treated with timolol. Based on the dissociation of IOP reduction and visual field prognosis, we postulate that for successful treatment in glaucoma not only the amount of IOP reduction is relevant but also the drug by which the reduction is achieved. This seeming paradox phenomenon highlights that ocular hypotensive drugs have relevant effects on GON other than IOP-related. Some of these effects on retinal ganglion cells (neuroprotection) or on ocular blood flow are mediated by calcium- and sodium channels.

Future studies on glaucoma treatment should focus on their effect on visual field function, and not just on IOP. This should particularly be considered when comparing drugs from different classes.

Contents

* Corresponding author. Department of Ophthalmology, University Hospital of Basel, Mittlere Strasse 91, P.O. Box CH-4031 Basel, Switzerland. Tel.: +41 61 265 8781; fax: +41 61 265 8652.
E-mail address: mgrieshaber@uhbs.ch (M.C. Grieshaber).

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1. Introduction

Glaucoma, the most common optic neuropathy (GON) is characterised by typical changes in the optic nerve head (ONH) and corresponding visual field defects. Morphologically, GON implies a loss of retinal ganglion cells and their axons, but also activation of glial cells and tissue remodelling. Further, premature aging of the mitochondria, oxidative stress and an altered gene expression leading to a microenvironment in and around the ONH in which the survival probability of the neural axons is reduced may play a role in the pathomechanisms. The structural changes of the ONH have long been described, but there is still debate about the pathogenesis of this disease. The main risk factor is an intraocular pressure (IOP) that exceeds the tolerance of the ONH. However, not all patients with increased IOP develop neuronal damage and not all patients with GON have an increased IOP. These facts challenge the pathophysiological concept of GON based only on IOP. In addition, there is mounting evidence of insufficient blood supply to the eye associated with GON either due to vascular dysregulation and/or systemic arterial hypotension (Flammer et al., 2002; Pache and Flammer, 2006). It is likely that vascular risk factors may by themselves lead to GON or they render the eye more sensitive to IOP, thus being interrelated.

What are the therapeutic implications? Among the multiple risk factors, an increased intraocular pressure (IOP) is of utmost importance. IOP reduction is also the most frequent goal for glaucoma therapy. For this reason, IOP is often taken as a surrogate for the treatment success of GON.

Indeed, IOP reduction in ocular hypertensives (OHT) reduced the probability for a conversion to primary open angle glaucoma (POAG) (Higginbotham et al., 2004, Kass et al., 2002). Further, reducing IOP decreased the risk of progression of GON in POAG patients (Heijl et al., 2002). In the Early Manifest Glaucoma Trial (EMGT), the risk of progression decreased by about 10% with each mmHg of IOP reduction from baseline to the first follow-up, and patients treated had half of the risk of progression of control patients (Leske et al., 2003, Leske et al., 2007). The collaborative normal-tension glaucoma (NTG) study demonstrated that an IOP reduction of at least 30% could significantly delay disease progression in the majority of patients at 5 years of follow-up (1998). These results also indicate – at least to a certain level – that there is also a "dose–response relationship": the lower the IOP, the lower the risk for progression.

Is IOP and IOP reduction always a good surrogate for a successful therapy of GON, and is this independent of the therapeutic modality to reduce IOP?

The fact that some glaucoma patients progress despite substantial IOP reduction, whereas other untreated patients do not progress (Coll NTG Study Collaborative Normal-Tension Glaucoma Study Group, 1998; Shigeeda et al., 2002) challenges the strong (causal) relationship between IOP and (visual field) progression. Likewise, IOP was not identified as a significant independent risk factor for progression in NTG (Drance et al., 2001), and stable findings of the ONH have been observed for up to 7 years in the majority of glaucoma suspects irrespective of IOP lowering therapy (Doshi et al., 2007).

Haefliger and Hitchings identified a subset (78%) of patients characterised by IOP independent damage in untreated asymmetric NTG patients (Haefliger and Hitchings, 1990) as they found a relationship between higher IOP and more severe visual field defect occurred only in 22%. An intra-individual comparison of visual field and IOP even revealed no correlation between IOP and visual field damage nor between the inter-ocular differences in IOP and in visual field damage (Orgul and Flammer, 1994). Half of the patients had more severe functional defects in the eye with the lower IOP. These results suggest that the visual field prognosis and progression may also depend on other factors than IOP (Daugeliene et al., 1998). Recently, the "low-pressure glaucoma treatment study group" evaluated prospectively the association between IOP and visual field asymmetry and found IOP asymmetry is unrelated to visual field asymmetry (Greenfield et al., 2007).

There is also some debate as to whether other IOP reducing interventions such as surgery or laser would have a similar impact on visual function like drugs when IOP is reduced by the same amount (2000, Ederer et al., 2004, Lichter et al., 2001, Stewart et al., 1986). While this is still not yet clear, even less is known with respect to different drugs (Flammer and Drance, 1983a). Should we convey more importance to the drug we achieve the target IOP or only to the target level of IOP? This question is of relevance in clinical practice when we choose between drugs, e.g. between modern but more expensive prostaglandin analogues and older and less expensive β-blockers. Unfortunately however, limited information is available in the literature comparing drug effects on long-term outcome of visual fields.

2. Is just the amount of IOP reduction relevant or also the method by which the reduction is achieved?

In order to answer to this crucial question, we analysed the literature concerning two different beta-blockers: betaxolol and timolol (Fig. 1).

The purpose of this analysis is not primarily to test whether one beta-blocker is superior to the other for clinical practice, but rather uses them as examples to answer a fundamental question: do ocular hypotensive drugs have additional long-term effects on visual function. In other words, is the rule – the lower the IOP, the better the visual field prognosis – always correct, and secondly – does it matter what drug is used to achieve the target IOP?

A number of studies have compared the *IOP lowering effect* of betaxolol and timolol. These publications are listed in Table 1. With regard to IOP reduction, betaxolol was less potent than timolol in most of the studies, sometimes equal but never more potent than timolol. Thus, there is strong evidence that the IOP reducing capacity of betaxolol was lower than that of timolol. If however, *visual field outcomes* were compared, betaxolol was either better or equal to but never worse than timolol in short- as well as in long-term studies (Table 2). In other words, betaxolol had a better or at

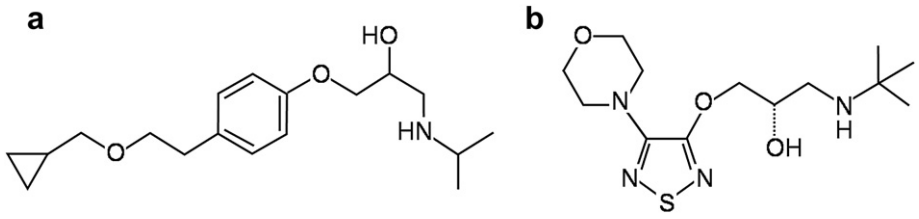

Fig. 1. The molecular structure of betaxolol and timolol.

least an equal impact on visual field prognosis than timolol despite a smaller IOP reduction.

From the studies listed in Table 2, we focus now on some of the longer-term studies. In a 24-month trial, the effects of betaxolol, timolol and pilocarpine on IOP and visual function were compared (Drance, 1998). All three drugs reduced IOP approximately to the same amount; betaxolol, however, had the best impact on visual fields when tested with short-wave automated perimetry. The visual field prognosis was also better in patients treated with betaxolol than with timolol in several other clinical studies running over a 2–4 year period (Araie et al., 2003; Kaiser et al., 1994; Tasindi and Talu, 1997), although IOP reduction was consistently greater with timolol (Fig. 2).

In a 7-year prospective study, the effect of three topical β-blockers used as monotherapy was determined (Watson et al., 2001). IOP reduction was similarly with timolol and carteolol, but lesser with betaxolol. However, there was a tendency for visual field outcome being better in the betaxolol group than in the timolol as well as in the carteolol group. These results are in line with the outcome of another double-blinded study: Miki and Miki (Miki and Miki, 2004) investigated the influence of a switch from timolol to betaxolol on IOP and visual field function in a four-year trial. Patients who have switched from timolol to betaxolol experienced an improvement in their visual field function after the fields had deteriorated during treatment with timolol over two years. If we take all these studies together, we can conclude that betaxolol was either better than or at least as effective as timolol in preserving visual field function even though betaxolol reduced the IOP less.

The analysis of structural parameters points to the same direction. The progression of retinal nerve fibre layer (RNFL) damage was less frequent, and a tendency towards better time course in patients treated with betaxolol than with timolol was observed (Vainio-Jylha et al., 2002). Further, the progression of RNFL damage did not correlate with the degree of IOP reduction (Vainio-Jylha et al., 2002). This is consistent with results of earlier, clinic based studies suggesting poor correlation between IOP level and glaucoma progression (Chauhan and Drance, 1992; Weber et al., 1993) in particular in NTG (Daugeliene et al., 1999, Ishida et al., 1998).

In order to understand all these facts, we will first discuss some principal aspects of the beta-adrenergic system with their stimulators and blockers before we go into a more detailed comparison between betaxolol and timolol.

3. Why is betaxolol less potent in reducing IOP than timolol?

3.1. β-Receptors in the eye

β-receptors occur widely throughout the eye, including the trabecular meshwork, lens epithelium and the ciliary-, choroidal- and even retinal arteries (Jampel et al., 1987, Polansky et al., 1989, Wax et al., 1989). The density of the β-receptors in the eye is particular high in the ciliary body (Nathanson, 1981; Wax and Molinoff, 1987) (Fig. 3) where they are predominantly found in the non-pigmented epithelium. β_1- and β_2-receptors belong to a receptor group that is positively coupled to adenylate cyclase through a stimulatory G-protein (Fig. 4).

Within the sympathetic presynaptic terminal, noradrenaline is stored in vesicles and discharged by a Ca^{2+}-dependent process. β-receptors often lack corresponding presynaptic area and are stimulated by circulating agonists. There is a relatively rich sympathetic supply to the ciliary muscle (Lograno and Reibaldi, 1986; Zetterstrom and Hahnenberger, 1988) and the ciliary vessels (Nyborg and Nielsen, 1995; Yu et al., 1992).

3.2. Difference in IOP reduction between betaxolol and timolol

IOP is determined on the one hand by the rate of aqueous formation and on the other hand by the resistance to outflow via

Table 1
Comparison of efficacy between betaxolol (B) and timolol (T) on IOP.

Authors and years	B superior	T superior	B = T
Stewart et al., 1986		+	
Allen and Epstein, 1986		+	
Feghali et al., 1988		(+)	+
Vogel et al., 1989		+	
Messmer et al., 1991		+	
Collignon-Brach, 1992		+	
Carenini et al., 1994		+	
Collignon-Brach, 1994		+	
Kaiser et al., 1994		+	
Harris et al., 1995		+	
Tasindi and Talu 1997		+	
Collignon and Collignon-Brach, 1997		+	
Drance 1998		+	
Vainio-Jylha and Vuori, 1999		+	
Evans et al., 1999		+	
Watson et al., 2001			+
Vainio-Jylha et al., 2002			+
Araie et al., 2003		+	
Rainer et al., 2003			+
Ohtake et al., 2004		+	
Sponsel, 2004			+
Miki and Miki 2004			+

Table 2
Comparison of efficacy between betaxolol (B) and timolol (T) on glaucomatous visual field function.

Authors and years	B superior	T superior	B = T
Messmer et al., 1991	+		
Collignon-Brach, 1992	+		
Collignon-Brach, 1994	+		
Kaiser et al., 1994	+		
Tasindi and Talu 1997	+		
Drance 1998	(+)		+
Vainio-Jylha and Vuori, 1999			+
Watson et al., 2001			+
Araie et al., 2003	(+)		+
Rainer et al., 2003	(+)		
Ohtake et al., 2004	+		
Sponsel, 2004	+		
Miki and Miki 2004	+		

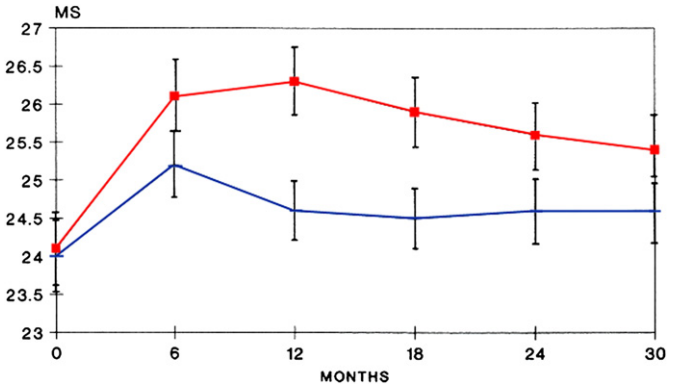

Fig. 2. Long-term visual field follow-up of glaucoma patients treated with beta-blockers. Averaged visual field index (Mean sensitivity [MS] ± SEM). Significantly larger averaged mean sensitivities were observed for the betaxolol patients (red) than for the timolol patients (blue) at 3, 6, 12, and 18 months. *Data from reference* (Kaiser et al., 1994).

conventional (i.e. trabeculocanalicular) and non-conventional (i.e. uveoscleral) pathways. In humans, the majority of studies showed that β-blockers have no effect on outflow facility (Diestelhorst and Krieglstein, 1989; Sonntag et al., 1978) despite the presence of β_2-receptors in the trabecular meshwork (Wax et al., 1989). This is due to the presumably negligible β-adrenergic tone in the trabecular meshwork. In simple words, if there is nothing to stimulate, there is nothing to be blocked.

In the ciliary body epithelium, β-receptors are widely distributed and β_2-receptors are much more common than β_1-receptors. Beta-blockers inhibit aqueous secretion by their action on the β_2-receptors of the ciliary processes (Bromberg et al., 1980; Nathanson, 1981). In general, β-adrenergic stimulation leads to an increase in 3′,5′ cyclic monophosphate (cAMP) production and β-receptor blockade leads to a reduction of cAMP. *Timolol* is a powerful *β_1- and β_2- blocker*, whereas *betaxolol* is a relative *selective β_1-blocker*. Thus, the fact that non-selective timolol reduces the IOP more than β_1-selective betaxolol is obvious. It is rather surprising however, that the difference in IOP reduction between betaxolol and timolol is not very large. One explanation could be that betaxolol is not totally specific for β_1-receptors (Nathanson, 1988), but also blocks to β_2-receptor to some extent. This is particularly relevant in high concentrations. Further, IOP reduction could be achieved not only by blocking the β-receptors but also by interaction of the beta-blockers with other receptors. For instance, serotonin (5-HT_{1A}) receptors have been well studied in this context (Allen and Epstein, 1986; Vogel et al., 1989)

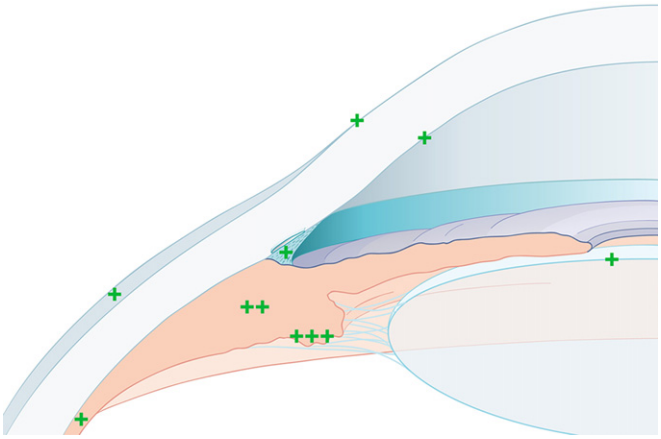

Fig. 3. The distribution of the beta receptors in the anterior segment. High (+++) to low (+) density of the beta receptors.

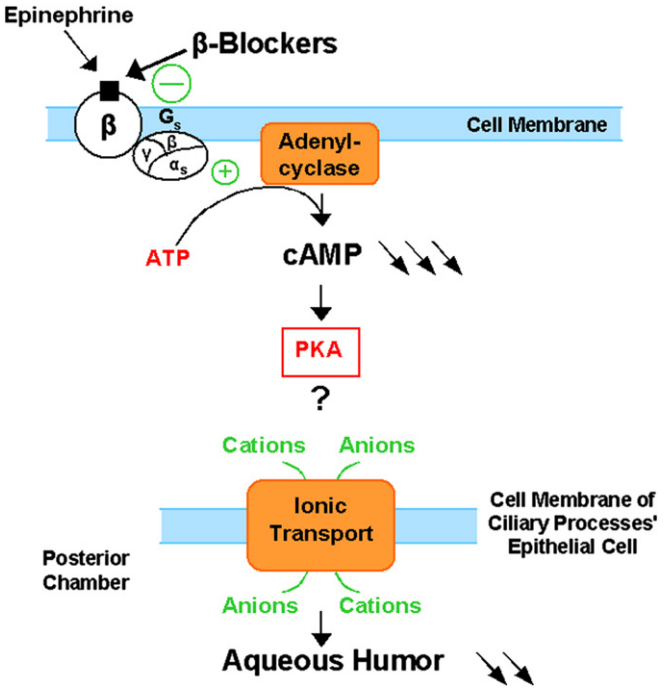

Fig. 4. Major pharmacological mode of action of β-blockers in the ciliary body. In competition with epinephrine for β-adrenoreceptors (β), β-blockers decrease intracellular concentration of 3′,5′ cyclic monophosphate (cAMP). Concomitantly, through a still poorly understood mechanism, they reduce aqueous humor production. Gs: stimulatory G protein. ATP: adenosine triphosphate. PKA: cAMP-dependent protein kinase. +: activation, −: inhibition. *Reprinted with permission from Verlag Hans Huber Bern, from reference* (Haefliger et al., 2000).

and will be discussed below. Further, both β-receptors agonists and antagonists may not only act at beta-receptors, but also at other receptors.

3.3. Specificity of β-receptors agonists and antagonists

Both beta-blockers, timolol and betaxolol, exist as enantiomers, so called D-, and L-enantiomers, which are stereoisomers that are nonsuperimposable mirror images of each other, much as one's left and right hands are "the same" but opposite (Fig. 5). Two enantiomers often have different chemical properties and effects. It is known that the L-enantiomers of β-adrenergic antagonists are more active than the D-enantiomers (Rahn et al., 1974). The L-enantiomer has a high affinity for the β-receptors, whereas the D-enantiomer has low affinity for the β-receptors (Tocco et al., 1976). While this is true for the receptors in the cardiovascular system, we may ask the question whether it is also the case for the receptors in the ciliary process. In rabbit and in human eyes studies, the potency of the D-enantiomer for instance was found to be similar to the one of the L-enantiomer of timolol in the ciliary processes of rabbits (Nathanson, 1988) suggesting a minor degree of stereo-selectivity in the ciliary process (Share et al., 1984). This may explain why D-enantiomers of beta-blockers, e.g. D-timolol, are as effective as the L-enantiomers in decreasing aqueous production (Liu and Chiou, 1981) and why D-enantiomers are more potent in reducing IOP than expected (Rowland and Potter, 1981). However, to the best of our knowledge, the difference between the D- and L-enantiomer has not been assessed in betaxolol.

3.4. Serotonin receptors

Serotonin (5-hydroxytryptamine, or 5-HT) is a monoamine neurotransmitter synthesised in serotonergic neurons in the

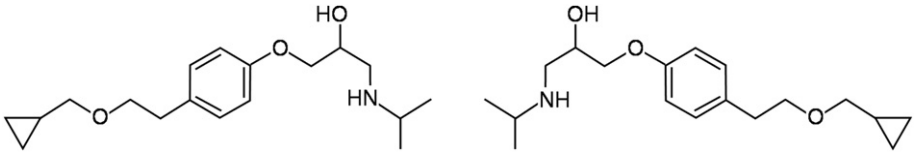

Fig. 5. D- and L- enantiomer of betaxolol.

central nervous system (CNS) and enterochromaffin cells in the gastrointestinal tract of humans. In the eye, serotonin is produced in the retina, in the iris and in the ciliary body (Barnett and Osborne, 1993; Tobin et al., 1988). Four classes of serotonin receptors termed 5-HT_1 5-HT_2, 5-HT_3, 5-HT_4 have been characterised (Frazer et al., 1990). It is to note that the 5-HT_{1A} subtype is *negatively* coupled to the adenylate cyclase-cAMP cascade (Frazer et al., 1990; Peroutka, 1990) in the rabbit- and in the human iris-ciliary body (Barnett and Osborne, 1993; Chidlow et al., 1998). This is of significance since the formation of aqueous humour in the ciliary body epithelium is cAMP dependent (Bartels et al., 1987; Kaufman, 1987; Sears, 1985) and indeed, the 5-HT_{1A} receptors are actively involved in the regulation of IOP as shown in rabbit eyes (Chidlow et al., 1999, Chu et al., 1999).

Studies from Martin et al. (Martin et al., 1988) showed that there is a correlation between IOP and the content of serotonin in the human aqueous humour. While stimulation of beta-receptors increased the IOP, stimulation of serotonin receptors decreased IOP. Serotonin agonists such as 8-hydroxydipropylaminotetralin (8-OH DPAT) and flesinoxan lowered the IOP in ocular hypertensive eyes of rabbits and humans (Chidlow and Osborne, 1997; Chidlow et al., 2001; Costagliola et al., 1991; Mastropasqua et al., 1997; Tekat et al., 2001).

3.5. Comparison between β_2-receptor and 5-HT_{1A} serotonin receptor

As we have seen before, the β_2-receptor and the 5-HT_{1A} serotonin receptor have an opposite effect on the adenylate cyclase-cAMP cascade in the ciliary body thereby modulating the IOP. The question comes up whether β-blockers have an effect on the serotonin receptors, interfering with the β-adrenergic system. In this section, we look first at the structural similarity of β_2-receptor and the 5-HT_{1A} serotonin receptor and then their impact on IOP.

3.5.1. Molecular analogy of β_2-receptor and the 5-HT_{1A} serotonin receptor

The genomic clone of a 5-HT serotonin receptor, called G-21, was identified by screening a human genomic library at reduced stringency with a probe corresponding to the sequence of the human β_2-receptor (Kobilka et al., 1987). The name G-21 was given as this clone contains genes encoding a G-protein-coupled receptor. The protein product of that clone (G-21) was found by means of radioligand-binding studies to have all the typical ligand-binding characteristics of the 5-HT_{1A} serotonin receptor (Fargin et al., 1988). Of interest, the G-21 DNA contained an open reading frame encoding amino acids with the characteristics of G protein-coupled receptors like the β-receptor. Within the transmembrane domains, the homology between the G-21 and the human β_2-receptor was towards 50% (Fargin et al., 1988).

3.5.2. Affinity of β_2-blockers for 5-HT_{1A} serotonin receptor in the ciliary body

Due to the molecular similarity of the β_2- and the 5-HT_{1A} receptor in the ciliary body (Tobin et al., 1988), β-blockers have some affinity for the 5-HT_{1A} receptors in the ciliary processes (Inoue-Matsuhisa et al., 2003). In a study performed by Osborne and Chidlow (Osborne and Chidlow, 1996), timolol (and propranolol) had a greater affinity for the 5-HT binding site in the ciliary processes of the rabbit eye than betaxolol (Fig. 6). The ability of a particular β-blocker to bind to 5-HT_{1A} serotonin receptor was found to be dependent upon the spatial occupancy of the amino-oxypropanol chains of the β-blocker but was unrelated to the affinity to the β_1- or β_2-receptor (Langlois et al., 1993).

3.5.3. Effects on IOP

The comparative affinity of β-blocker to 5-HT_{1A}-receptor and to β_2-receptor in ciliary processes is reflected in their effects on IOP. Topical application of a 5-HT_{1A} agonist such as 8-OH-DPAT lowered the IOP in rabbits significantly (Osborne and Chidlow, 1996). Conversely, blocking the 5-HT_{1A} receptors in the ciliary processes increased the IOP and thereby hampered the β_2-receptor effect on IOP. Further, timolol decreased the serotonin content of the aqueous humour (Brennan et al., 1990).

Osborne and Chidlow (Osborne and Chidlow, 1996) found that timolol has about a 100 fold higher blocking capacity for the serotonin receptor than betaxolol, and hypothesised that simultaneous blockage of the β_2- and 5-HT receptors have opposite effects on cAMP production in the ciliary epithelium (Fig. 7).

Since β_1-selective betaxolol has a low affinity not only for the β_2- but also for 5-HT serotonin receptors, the resulting effect on cAMP

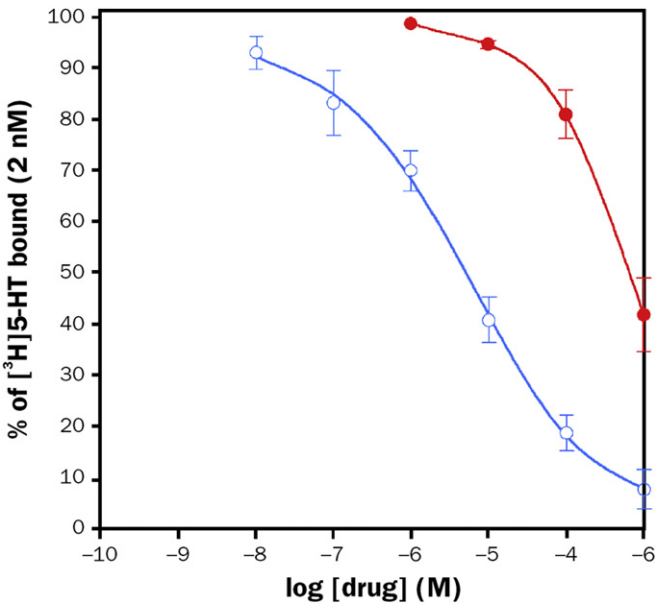

Fig. 6. Relative affinity of betaxolol and timolol for the 5-HT1A-receptor. Competitive curves for inhibition of [3H]5-hydroxytryptamine-specific binding by timolol (blue) and betaxolol (red) to membrane homogenates of rabbit iris-ciliary body. Data are mean values from three separate experiments performed in triplicate. Nonlinear regression analysis of drug interactions with [3H] 5-hydroxytryptamine binding sites in rabbit iris-ciliary body indicate the majority of binding is to a population of sites with 5-HT1A receptor pharmacological profile with a smaller binding component to a second population of sites. *Reprinted in part with permission from Verlag Hans Huber Bern, from reference* (Bron et al., 2000).

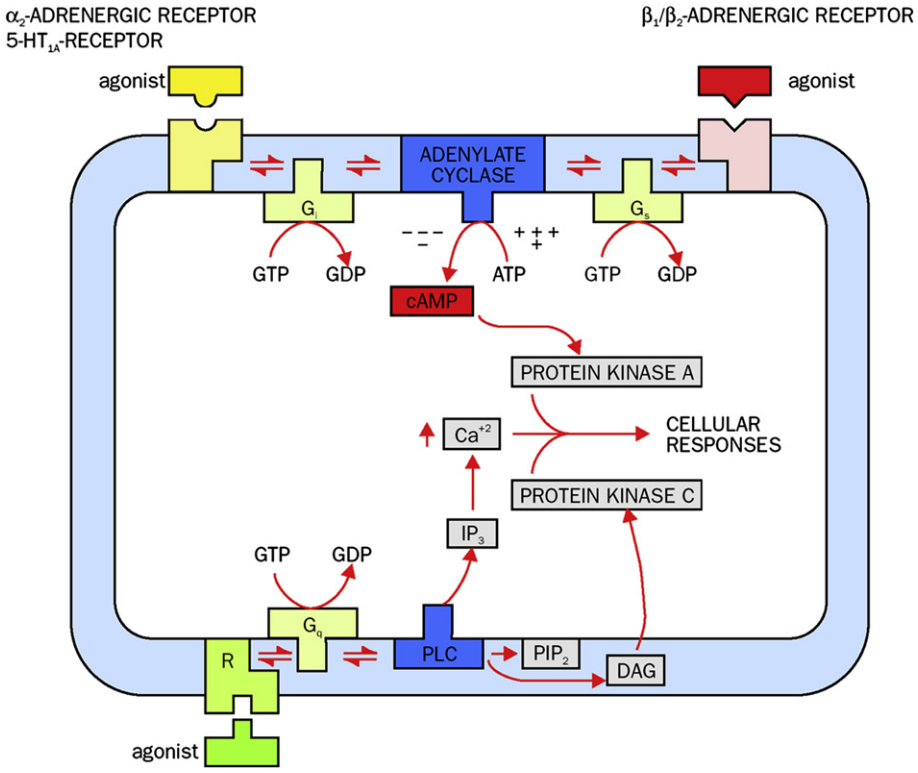

Fig. 7. Schematic drawing of second messengers associated with selected beta-adrenergic and serotonergic receptors. The β1–β2 receptors are positively coupled to adenylate cyclase. Stimulation causes a rise in cAMP. The α2- and 5HT1A-receptors are negatively coupled to adenylate cyclase. Stimulation causes a fall in cAMP production. The α1- and 5HT2A-receptors are coupled to phospholipase C. Activation leads to an increase in cellular protein kinase C and calcium. DAG = DIACYLGLYCEROL, Ip3 = INOSITOL 1,4,3-TRIPHOSPHATE, PI = PHOSPHATIDYLINOSITOL, PIP = PHOSPHATIDYLINOSITOL 4-PHOSPHATE, PIP2 = PHOSPHATIDYLINOSITOL 4,5-BISPHOSPHATE, PLC = PHOSPHOLIPASE C, 5-HT = SEROTONIN, α; β = ADRENERGIC. *Reprinted in part with permission from Verlag Hans Huber Bern, from reference* (Bron et al., 2000).

is comparable to the one of timolol which has a high affinity for both receptors. This explains partially why β_1-selective betaxolol is only slightly less effective than timolol in reducing IOP despite its low binding affinity to β_2-receptor (Fig. 8).

4. Why is betaxolol at least as good as timolol in preserving visual field function?

There is substantial evidence that risk factors other than IOP play also an important role in the pathogenesis of glaucoma (Flammer et al., 1999; Flammer et al., 2002; Pache and Flammer, 2006). Among them, a disturbed ocular blood flow (OBF) has in particular been implicated (Grieshaber and Flammer, 2005). In short-term studies, a better OBF showed an improvement of the visual field function. The visual response to increased OBF is independent of the way OBF is improved. The bottom line of functional improvements following breathing carbon dioxide (Pillunat et al., 1994), intake of calcium-antagonists (Gaspar et al., 1995) or acetazolamide (Flammer and Drance, 1983a,b) is that all these substances improve OBF. There are indications that improvement of OBF may be beneficial in long-term treatment of GON (Ishida et al., 1998), although definite proof is missing.

A basic question concerning anti-glaucomatous drugs is whether these drugs have beside the IOP lowering property additional properties that may contribute to visual function, e.g. why has betaxolol a better or an equal impact as timolol on visual fields despite a less IOP reduction of betaxolol. In the following, we will discuss first the effect of betaxolol and timolol on OBF in in-vitro, animal and clinical studies. Secondly, we elaborate on the neuroprotective potential of these two beta-blockers.

4.1. Do betaxolol and timolol have a different effect on ocular blood flow?

In most blood vessels, β_2-adrenergic stimulation causes vasodilatation, whereas stimulation of α_1-adrenoreceptor causes vasoconstriction. There were some debates about the vasoconstrictive potential of beta-blockers, as during β_2-adrenoreceptor blockade α_1-mediated effects of endogenous adrenergics are no longer opposed. However, whether β-blockers actually exhibit such vasoconstriction in the posterior segment of the eye depends on whether or not functional β-adrenoreceptors are present in the arteries. This was extensively studied on the posterior ciliary- and retinal arteries of both animal (Hester et al., 1994; Nielsen and Nyborg, 1989; Nyborg and Nielsen, 1995; Yu et al., 1998a) and human cadaver eyes (Nyborg and Nielsen, 1995). The fact that β-adrenergic agonists failed to induce significant vasodilatation, indicates that β-receptors are too few in number in the posterior ciliary- and retinal arteries (Hoste, 1999). Therefore, β-blockers are unlikely to have an adverse vasoconstrictive effect in the posterior segment of the eye through their β-adrenoreceptor blocking activity (Hoste, 1999). In contrast, various studies found β-blockers have even a vasodilatatory effect (Dong et al., 2006; Hester et al., 1994; Hoste and Sys, 1994; 1998; Yu et al., 1998a) *not explained by the β-adrenoreceptor blocking activity* (Brogiolo et al., 2002, Melena et al., 1999, Melena et al., 2001). This effect was attributed to the *calcium* (Ca^{2+}) *-channel blocking* properties of β-blockers. This is of vital importance since Ca^{2+} and calcium channel blockers (CCBs) play crucial roles in the regulation of blood flow. In the following excursus, we discuss the role of Ca^{2+} and CCBs in general and their impact on OBF; thereafter the effect of betaxolol and timolol on OBF.

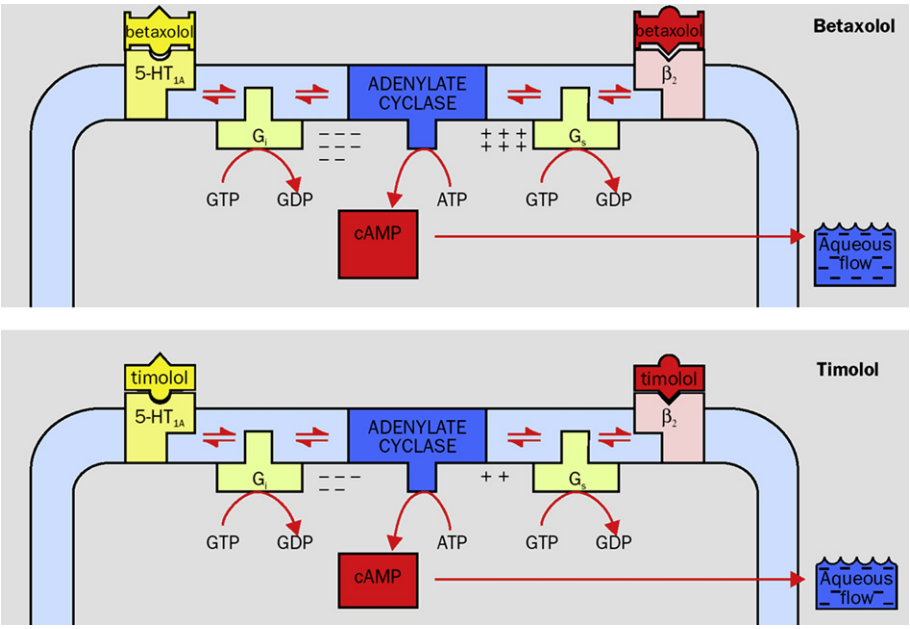

Fig. 8. Hypothesis to explain the mode of action of beta-blocker drugs on aqueous secretion via a combined action on the β2 receptor and the 5-HT1A receptor present in the ciliary processes. The 5-HT1A (serotonin receptor) is negatively coupled to adenylate cyclase via a G-protein (Gi). The β2 receptor is positively coupled to adenylate cyclase via a GS-protein. Aqueous secretion is conceived to be influenced, in addition, by input from other receptors. In this schematic diagram the aqueous flow rate is represented as dependent on the amount of cAMP produced in the cell. The β1-selective blocker betaxolol binds weakly to both receptors. The net effect is a moderate reduction in cAMP production and a moderate decrease in aqueous flow (top). The β1/β2-blocker timolol binds more strongly to each receptor, resulting in a slightly greater reduction in cAMP and a slightly greater fall in aqueous flow (bottom). *Reprinted in part with permission from Verlag Hans Huber Bern, from reference* (Bron et al., 2000).

4.2. Calcium, calcium channel blocker and blood flow

Calcium (Ca^{2+}) influx in the vascular smooth muscle cells and pericytes leads to vasoconstriction. Ca^{2+} influx can be diminished, for instance, by blocking the voltage-dependent Ca^{2+}-channels. There are several different kinds of high-voltage-gated calcium channels such as L-, N-, P-, Q-, R- and T-type. They are structurally all similar, but not identical. Among the different types of calcium channels, the L-type occurs predominantly in the vascular smooth muscle. The calcium channels are regulated in part by both the potential of the cell membrane and the G-proteins. The G-proteins, in turn, are activated by various hormones receptors such as ET-1 (Fig. 9). The stimulation of ET receptors on smooth muscle cells or pericytes increases cytoplasmic calcium, both by influx into the cell, as well as by liberation of calcium from the internal storage.

Extrapolating from general vascular medicine we expect no or little effect of CCBs on healthy, normally regulated vessels. CCBs act however as vasodilator in pathological constricted vessels. Some CCBs like *nimodipine* are more *lipo-soluble* and therefore cross the blood-brain- and blood-retinal-barrier, while others like *nifedipine* are more *water-soluble* and therefore have little effect on the circulation of the brain or the retina. For glaucoma therapy, the ONH is of vital importance. Interestingly, the ONH has an incomplete blood-brain-barrier which is further disturbed in glaucoma (Grieshaber and Flammer, 2007). Due to the diffusion from the neighbouring choroid, not only lipo-soluble but also water-soluble CCBs have access to the ONH explaining why both types of CCBs might be beneficial in the therapy of glaucoma patients.

Analysing the ophthalmic literature however, the effects of CCBs on ocular blood flow (OBF) in healthy subjects and glaucoma patients are not conclusive. In a colour Doppler imaging study on patients with NTG, the blood flow velocities in the central retinal-, posterior ciliary-, and ophthalmic artery did not change after treatment with nifedipine (30 mg/day) for 3 weeks (Geyer et al., 1996). This result was confirmed by another study on NTG patients when nifedipine was administrated for 6 weeks (Wilson et al., 1997). In a longer-term study of 6 month-treatment with nifedipine, similar results were found in NTG patients (Harris et al., 1997). The contrast sensitivity was increased only in patients who had improved retrobulbar hemodynamics; no difference in blood flow was however detected in the majority of patients. Likewise, nifedipine had no significant effect on blood vessels and OBF in healthy subjects (Gaspar et al., 1994, Schmidt et al., 1996).

The reported impact of nimodipine on the retinal circulation is also inconsistent. Whereas single-dose application of nimodipine (30 mg) normalised impaired retinal capillary blood flow (Luksch et al., 2005), Piltz and coworkers (1998) (Piltz et al., 1998) failed to demonstrate any effect on blood flow in the macula in

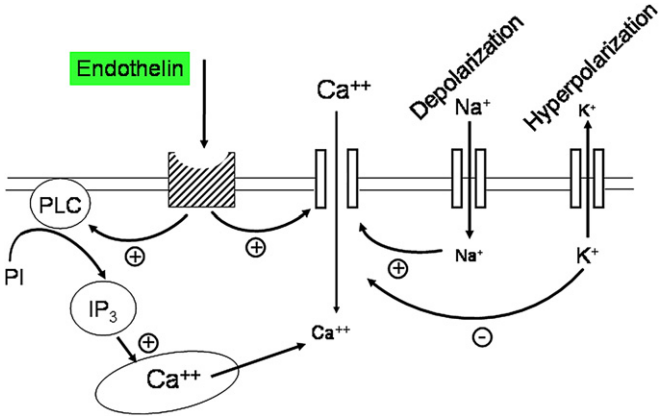

Fig. 9. Regulation of calcium channel. The calcium channels are regulated in part by both the potential of the cell membrane and the G-proteins. The G-proteins, in turn, are activated by various hormone receptors such Endothelin. *R*eproduced with permission from Flammer J, Die Behandlung des Normaldruckglaukoms mit Kalziumantagonisten. *Search on Glaucoma 5: 3–7, 1997.*

a double-masked, placebo-controlled crossover study with a 60 mg dose. In contrast, all studies using nilvadipine, another L-type CCB, detected a beneficial effect on OBF (Niwa et al., 2000, Tomita et al., 1999, Yamamoto et al., 1998). The blood flow velocities in the ONH and the retrobulbar vessels were consistently increased and the vascular resistance was reduced when nilvadipine was used at very low doses (2 mg b.i.d.) (Tomita et al., 1999, Yamamoto et al., 1998). To date, little is known about the effect of magnesium, a physiologic CCB, on blood flow. Gaspar et al. found a slight improvement in the peripheral blood flow measured with nailfold-capillary microscopy (Gaspar et al., 1995); however, no study has investigated the effect on OBF.

Importantly, we have to keep in mind that an effect of any drugs like CCBs on OBF is only likely if a vascular problem, for instance a vascular dysregulation is present, whereas a drug-mediated effect is very unlikely to be expected if no such dysregulation is present (Drance et al., 1988). This may also explain, in part, the contractive results in healthy and glaucoma patients. Further, we have seen that some CCBs may improve the OBF, whereas the majority of CCBs is rather neutral in this regard. The validation and interpretation of these results should be taken with a pinch of salt since for several reasons: First, most studies did not distinguish subjects or patients with from those without a vascular problem; second, not all patients with glaucoma have a vascular regulatory problem, although a vascular dysregulation is often seen in patients with NTG; third, CCBs in different dosages have variable effects on OBF and fourth, OBF cannot be measured directly with most of the current available devices. Beta-blockers have unique calcium-channel blocking properties of all IOP lowering drugs that could explain the IOP unrelated impact on OBF.

4.3. In-vitro *evidence of vascular effects of β-blockers*

Studies investigating the effect of β-blockers on vessels showed that all β-blockers have a tendency to dilate the vessels (carteolol, levobunolol and timolol and betaxolol) with betaxolol having the greatest effect (Hester et al., 1994; Hoste and Sys, 1994; Melena et al., 2001; Yu et al., 1998a). For this reason, betaxolol has been in particular well studied. Betaxolol was found to relax retinal (Bessho et al., 1991; Hoste and Sys, 1998; Hoste, 1999; Yu et al., 1998b) and posterior ciliary arterioles (Hester et al., 1994), especially when the vessels were precontracted with potassium-chloride (Dong et al., 2006; Hoste and Sys, 1994; Hoste, 1999) or with endothelin-1 (ET-1) (Yu et al., 1998b). The latter observation is of particular interest in glaucoma, since ET-1 is a very potent vasoconstrictor and plays a role in the vascular dysregulation (Flammer et al., 2002, Grieshaber et al., 2007). In addition to the vascular effect, important functions have been attributed to ET-1 in glaucoma. For example, ET-1 modulates the axoplasmatic flow in the optic nerve (Stokely et al., 2005, Taniguchi et al., 2006) and enhances the glutamate-induced retinal cell death in glaucoma (Kobayashi et al., 2005). ET-1 also induces astroglial proliferation (Prasanna et al., 2002) and modulates the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs in astrocytes of the ONH (He et al., 2007). These processes are actively involved in glaucomatous damage and tissue remodelling. ET-1 further belongs to humoral factors that modulate the blood-brain-barrier (Chen et al., 2000, Narushima et al., 1999, Narushima et al., 2003). A disturbed blood-brain-barrier was proposed to be relevant in the pathogenesis of optic disc haemorrhages (Grieshaber et al., 2006; Grieshaber and Flammer, 2007).

In conclusion, in-vitro studies indicate that β-blockers have (mild) vasodilatatory properties in the ciliary- and retinal arteries by blocking the Ca^{2+}-channels to some extent. Betaxolol stands out for its largest Ca^{2+}-channel blocking potency of all β-blockers.

4.4. Evidence of vascular effects of β-blockers in animal studies

Differences of animal to in-vitro studies can be partially explained by the pharmacokinetics. There is evidence that β-blockers reach the back of the eye in a sufficiently high concentration to exhibit their vasoactive properties (Osborne et al., 1999a); the way they reach that site of action is, however, still debated. β-blockers are more lipophilic than hydrophilic substances. Some authors have suggested that diffusion through the cornea and the vitreous body may play a minor role because of the lipophilicity of the drugs (Tan et al., 2002). Others found, however, high concentrations of betaxolol in the aqueous humour and the vitreous body of rabbits (Dahlin et al., 2000, Osborne et al., 1999a) as well as in monkeys and humans (Hollo et al., 2006). A relatively high concentration of betaxolol was also found in untreated fellow eyes suggesting the systemic blood circulation being a major transport route of β-blockers to the posterior segment of the eye (Osborne et al., 1999a). The concentration of betaxolol found in these eyes was even manifold higher than the minimum concentration necessary for vasorelaxation (Dahlin et al., 2000). However, the concentration of betaxolol and of timolol was comparable in the periocular and intraocular tissue of fellow eyes (Salminen and Urtti, 1984; Schmitt et al., 1980).

In regard to OBF, betaxolol tends to decrease the vessel resistance in the retina and the choroid whereas timolol tends to increase it (Kiel and Patel, 1998; Sato et al., 2001). Following intravitreal injection of ET-1 in rabbits, betaxolol significantly blunted the decrease in choroidal blood flow (Kim et al., 2002). In another study, blood flow velocity in the ONH was even increased in the untreated contralateral fellow eyes when compared to baseline, however, not as high as in the eyes treated with betaxolol (Araie and Muta, 1997). Having said that, no impact of timolol and betaxolol on OBF (Orgul et al., 1995), or even a decrease in OBF was found by others (Chiou and Chen, 1993).

Taking together, topically applied β-blockers reach the posterior segment either through local diffusion or via blood circulation after systemic absorption or both. Betaxolol tends to have a vasodilatatory and whereas timolol has a neutral effect of the blood flow. One should keep in mind however that most of this knowledge results from animal studies (e.g. rabbits). Blood and tissue levels resulting from systemic absorption are greater in animals than in humans because of the small body mass and volume distribution (Osborne et al., 1999b, Wood et al., 2001). Extrapolations to humans are therefore difficult. Relevant clinical studies investigating the effect of β-blockers on OBF in humans will be discussed in the following.

4.5. Evidence of vascular effect of β-blockers in humans

Clinical studies indicate that betaxolol has, in general, a more beneficial effect on OBF than timolol (Carenini et al., 1994, Harris et al., 1995, Schmetterer et al., 1997, Turacli et al., 1998). Betaxolol increased blood flow velocity and decreased resistive index in ocular and retrobulbar vessels of glaucoma patients in short- (Altan-Yaycioglu et al., 2001, Gupta et al., 1994) and in longer-term (6–12 months) studies (Evans et al., 1999, Turacli et al., 1998), whereas timolol even induced some vasoconstriction of retinal arteries (Martin and Rabineau, 1989), reduction of the end-diastolic velocity in the ophthalmic artery (Nicolela et al., 1996), and an increase in the resistive index of posterior ciliary arteries (Altan-Yaycioglu et al., 2001). Similarly, the peripapillary blood flow and ocular pulse amplitude remained unchanged with betaxolol, but decreased with timolol in a study using scanning Doppler flowmetry (Haefliger et al., 1999) or laser interferometry (Schmetterer et al., 1997), respectively. Betaxolol also improved the microcirculation in the macula (Tamaki et al., 1999), and was associated with a higher perimacular leukocyte velocity than timolol (Sponsel et al., 1997). Studies which examined

the influence of a switch from timolol to betaxolol on OBF are however not conclusive. Some found a significant increase in the blood flow velocity in the retrobulbar vessels on betaxolol (Bergstrand et al., 2001), whereas others found no different effect between betaxolol and timolol on retrobulbar (Harris et al., 1995), retinal or choroidal blood flow (Rainer et al., 2003).

Recapitulating, clinical studies indicate that betaxolol has a positive effect on OBF, whereas timolol most probably has a rather neutral effect. The exact validation and interpretation of the published data are however difficult because of different types of patients included and different methods used to measure OBF.

5. Do β-blockers play a role in the neuroprotection in glaucoma?

The term neuroprotection refers to the use of any treatment modality that prevents or retards apoptosis-associated neuronal cell death. It is achieved by favourably altering the balance between survival and death processes resulting in the recovery of neurons and thus of the structure and function of the nervous system. In recent years, neuroprotection has become a potential treatment option in glaucoma (Yucel et al., 2006) and CCBs have been suggested to be a candidate. This chapter deals with the role of Ca^{2+} in retinal ganglion cell death, and the capacity of CCBs including beta-blockers in neuroprotection.

5.1. The role of Ca^{2+} for the retinal ganglion cells death

Calcium plays a crucial role in the signal transduction in the cell. Ca^{2+} is therefore exactly regulated by calcium channels and by pumps, and the homeostasis of the intracellular Ca^{2+} is very complex. Ca^{2+} overload in the cell results from Ca^{2+} influx through both, receptor-operated and voltage-gated L-type Ca^{2+} channels, as well as via the stimulation of the ionotropic glutamate receptors (Osborne et al., 1999b, Osborne et al., 2005) (Fig. 10). Any increase of intracellular Ca^{2+} can activate degradative processes resulting in break-down of membranes and cytoskeletal elements, which lead to ganglion cell death (Kristian and Siesjo, 1998; Sasaki and Kaneko, 2007). In addition, oxidative stress is also involved in this process, the causality and the sequence of the events is not clear yet (Flammer and Mozaffarieh, 2007). Beside Ca^{2+} overload, sodium (Na^+) channels play an important contributory role in the ganglion cell damage. Na^+ can influx directly into the cell, or through non-specific pores. The resultant rise in Na^+, coupled with membrane depolarisation, leads to reversal of the Na^+/Ca^{2+}-exchanger linked to non-N-methyl-D-aspartic acid (NMDA) receptors; (Li and Stys, 2000; Smith et al., 2000) which imports damaging quantities of Ca^{2+} into the cell.

5.2. Calcium-channel blockers and neuroprotection

All drugs that prevent Ca^{2+} overload by modifying the entry of Ca^{2+} into the cell are promising candidates for neuroprotectants in glaucoma therapy (Garcia-Valenzuela et al., 1995; Kerrigan et al., 1997; Nickells and Zack, 1996; Okisaka et al., 1997).

Free radical and excessive increase of excitatory amino acids, such as glutamate, are thought to be involved in the initiation of the retinal and ganglion cell degeneration. The precise underlying sequence of events is not understood. Glutamate, for instance, performs a dual role. It is an excitatory neurotransmitter under normal condition and a toxic substance to neuronal cells when present in excess during ischemia (Ju et al., 2008, Louzada-Junior et al., 1992, Wang et al., 2004). Activation of NMDA receptors leads to a depolarisation of the neurons and voltage-dependent Ca^{2+}-channels become activated. In animal studies, NMDA receptor blockers such as MK-801 have partially prevented the loss of retinal ganglion cells caused by elevated IOP (Chaudhary et al., 1998; Lam et al., 1997; Osborne, 1999) and CCBs such as flunarizine, verapamil, nicardipine and lomerizine had a beneficial effect by blunting the number of retinal ganglion cells death (Crosson et al., 1990; Hara et al., 2004; Jensen, 1995; Osborne et al., 2002; Takahashi et al., 1992; Toriu et al., 2000).

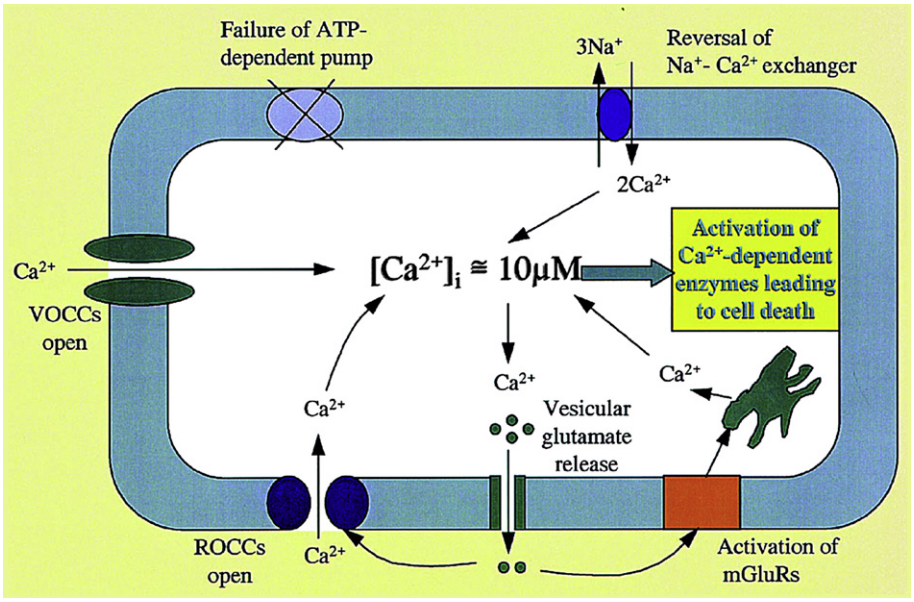

Fig. 10. Effect of hypoxia/ischemia on intracellular calcium. Cellular changes as result from an ischemic insult to a hypothetical excitatory retinal neuron. Cessation of ATP synthesis results in failure of ATP-driven membrane pumps. The resulting changes in intracellular ion concentrations causes membrane depolarisation, reversal of Na^+/Ca^{2+}–exchange, opening of voltage operated calcium channels (VOCCs) and a release of neurotransmitters. For neurons expressing the requisite receptors for glutamate, there will be an associated activation of metabotropic glutamate receptors (mGluRs) and a mobilization of calcium from intracellular stores as well as an opening of receptor-operated calcium channels (ROCCs). The summation of these effects is the increase of $[Ca^{2+}]i$ to micromolar levels and an activation of multiple calcium-dependent enzymes which may lead to necrotic cell death. *Reprinted with permission from Verlag Hans Huber Bern, from reference* (Osborne et al., 2000).

5.3. Calcium-channel blockers and visual function

Improved visual field following systemic CCBs, e.g. nifedipine, was suggested to be related to improved ocular circulation (Flammer, 1992; Gasser and Flammer, 1990; Kitazawa et al., 1989). Subsequent studies confirmed the hypothesis of improved visual fields following CCBs. Even a favourable prognosis for glaucoma patients on CCBs has been postulated in some studies (Daugeliene et al., 1999, Ishida et al., 1998, Netland et al., 1993) but not in all (Liu et al., 1996, Muskens et al., 2007). In prospective studies, brovincamine and nilvadipine delayed visual field deterioration in patients with NTG (Koseki et al., 1999, Koseki et al., 2008, Sawada et al., 1996) whereas nimodipine had a beneficial effect on contrast sensitivity (Bose et al., 1995). Whether the advantageous effect of CCBs on visual function derives from improved OBF or from neuroprotection is difficult to strictly distinguish. For instance, an enhanced contrast sensitivity in NTG patients was associated with changes in retrobulbar- and OBF (Chung et al., 1999, Harris et al., 1997, Luksch et al., 2005) whereas a significant increase in contrast sensitivity during treatment with nimodipine was measured without any significant change in OBF in a double-blind, placebo-controlled study (Boehm et al., 2003).

Likewise, the visual field and colour vision improved in patients of another study, although macular hemodynamics did not alter when the blue field entoptic simulation technique was used (Piltz et al., 1998).

Although a large number of studies have investigated the relationship between CCBs and visual function, several points need to be considered in the interpretation of these results. First, CCBs have an impact on OBF as earlier discussed and short-term improvements of visual field are therefore likely to result from an improved OBF. This can also easily be observed when the visual field improves following CCBs. Moreover, there is a correlation between visual function and systemic circulation as first noted by Gasser et al. in 1987 (Gasser and Flammer, 1987). They observed that in vasospastic patients and in NTG patients the visual field defects became aggravated by immersion of a hand in cold water and the scotomata improved after CCB was given (Gasser and Flammer, 1987) (Fig. 11). Second, some long-term studies compared the improvement of visual fields whereas others evaluated the prevention of visual field progression, e.g. rate of new scotomas. It is likely that the preservation of visual field in the long run is related more to a sustained neuroprotection than to OBF.

As we have mentioned earlier, the ganglion cell damage results not only from Ca^{2+} overload, but also from Na^{+} influx into the cell. The next section deals with Na^{+} and Na^{+}-channel blocker.

5.4. Sodium-channel blocker in glaucoma

The main mechanism of the damaging effect of ischemia to the optic nerve is not limited to Ca^{2+} influx (Fern and Ransom, 1997; Stys, 2004), but rather includes a general run-down of ionic gradients. Reduction of oxygen or glucose supply leads to a decline in the level of adenosine triphosphate (ATP) and failure of the Na/K-ATPase pump. Intra-axonal Na+ rises through leakage of this ion through Na + channels that remain open despite membrane depolarisation. Intracellular potassium is simultaneously lost through certain types of potassium channels (Chiu et al., 1999; Dodson and Forsythe, 2004; Stys et al., 1998). The increase in internal Na+, linked to membrane depolarisation, leads to the reversal of the $Na+/Ca^{2+}$ -exchange mechanism, which abnormally exports Na+ in exchange for Ca^{2+} influx. This contributes to Ca^{2+}-mediated damage (Orrenius et al., 1996; Stys and Lopachin, 1998) together with the rise in intra-axonal Ca^{2+} from influx through L-type voltage-dependent Ca^{2+}-channels (Brown et al., 2001). In addition, a small quantity of Ca^{2+} may enter directly through Na^{+} channels. It is obvious from the above-mentioned findings that CCBs alone are not efficacious enough to prevent the reversal of the Na^{+}/Ca^{2+}-exchanger, and to attenuate the cascade of excitotoxic events through Ca^{2+}-overload. Na^{+}-channel blockers are at least as crucial as the CCB at blunting the damaging effect of ischemia to the optic nerve, since it is the rise in internal Na^{+} that leads to all subsequent detrimental events. It has indeed been shown that some Na^{+} channel blockers such as certain anticonvulsants, antiarrhythmics and anaesthetics are to some extent neuroprotectants by inhibiting the Na^{+}/Ca^{2+}-exchanger (Garthwaite et al., 1999; Stys et al., 1992; Stys, 1995). The fact that Ca^{2+} was able to enter axons not only through Ca^{2+}-channels but also through Na^{+} channels further attributes importance to Na^{+} channels in optic nerve injury (Stys and Lopachin, 1998). A *combined* Na^{+}- and Ca^{2+}-channel blocker was therefore proposed to protect the ganglion cells from excitotoxic injury (Osborne et al., 2004). Interestingly, beta-blockers have been shown to be able to blunt the effect of ischemic events to the retina in animals (Chen et al., 2007, Cheon et al., 2002, Cheon et al., 2003, Osborne et al., 1999a, Wood et al., 2001), in spite of the fact that neurons lack of beta-receptor. In other words,

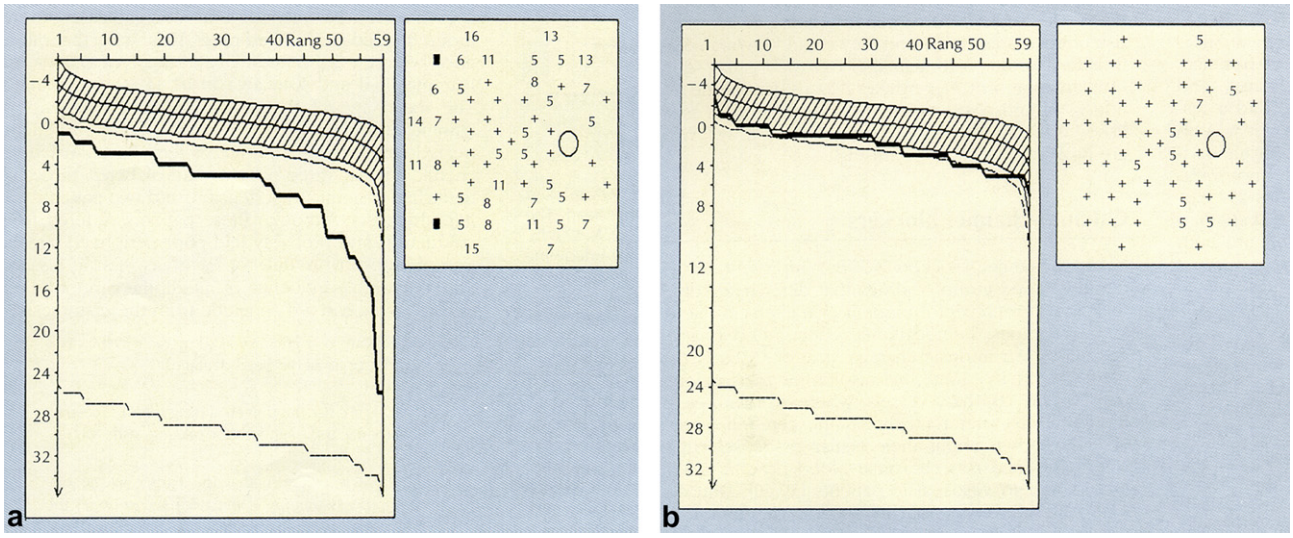

Fig. 11. The impact of CCB on a vasospastic patient challenged by cold stimuli. Dffuse visual field defects (Bébie curve, Octopus Program G1) in a vasospastic patient following immersion of a hand in cold water before (a) and after treatment with CCB (b). *Reprinted with permission from Documenta Ophthalmologica from reference* (Gasser and Flammer, 1987).

beta-blockers have properties apart from their action at the beta-receptor that allows them to act as neuroprotectants. Based on in-vitro studies, β-blockers have the unique feature of a combined Ca^{2+} and Na^{+} channel blocking activity of all glaucoma drug class (Chidlow et al., 2000, Melena et al., 2001, Wood et al., 2003).

5.5. β-Blockers and neuroprotection

In a laboratory study (Melena et al., 2001), both timolol and betaxolol showed an affinity for the L-type voltage-gated Ca^{2+} channel and were able to counteract the Ca^{2+} influx induced by NMDA receptor stimulation. Betaxolol however, had a much greater blocking activity for the Ca^{2+} channel (Melena et al., 2001) and was more effective than timolol in reducing the Na^{+} entry into neurones by direct interaction at the Na^{+} channel (Chidlow et al., 2000). This effect was observed already within an hour of topically applied betaxolol in rabbit eyes (Osborne et al., 1999a). The putative advantage of betaxolol over timolol in counteracting Ca^{2+}-overload was also observed in retinal cell cultures. Betaxolol showed a substantial positive effect on cell survival after excitotoxic insult, whereas timolol did not (Baptiste et al., 2002). This phenomenon can be explained by the fact that betaxolol interacts directly with a special site of the Na^{+} channel, the neurotoxin site 2, and inhibits Na^{+} influx more effectively than timolol (Chidlow et al., 2000, Osborne et al., 2004).

The neuroprotective action of betaxolol was also evident in animals which were treated with betaxolol before and after ischemia/reperfusion (I/R) (Cheon et al., 2002, Cheon et al., 2003). Histochemical examination demonstrated that the inner retinal layer was more susceptible to an induced I/R injury than the outer retinal layer (Cheon et al., 2002, Cheon et al., 2003, Ju et al., 2000, Osborne et al., 1997) which is similar to glaucomatous damage. Betaxolol attenuated retinal I/R damage in the rat even when it was administered after transient ischemia. Such attenuations of I/R damage point to a neuroprotective property of betaxolol (Cheon et al., 2003).

The neuroprotective potential of beta-blockers has also been evaluated with functional tests. In electrodiagnostics, a marked reduction of b-wave amplitude in the electroretinogram (ERG) is often seen in I/R damage and represents a reduced function of the Müller cell and bipolar cells. Betaxolol caused a significant attenuation of the reduced b-wave amplitude in rats (Wood et al., 2001) whereas timolol did not (Osborne et al., 2004). Betaxolol also increased the amplitude of b-wave (Uji et al., 2003) (Fig. 12).

Further, evidences of the neuroprotective effect of betaxolol are increased levels of brain derived neurotrophic factor mRNA (Wood et al., 2001) as well as a decreased intensity of neuronal and endothelial nitric oxide synthase (nNOS, eNOS) immunoreactivity (Cheon et al., 2002, Cheon et al., 2003) after betaxolol treatment in rats. The latter is relevant since massive production of NO is predominantly triggered by Ca^{2+} influx coupled through glutamate-induced in ischemic retina. It is to note, however, that I/R injury in experimental and animal studies are marked and acute, whereas I/R damage in human glaucoma is thought to be subtle but iterative over many years (Flammer et al., 2002; Flammer and Mozaffarieh, 2007; Grieshaber et al., 2007). Extrapolations to human glaucoma should be done with caution.

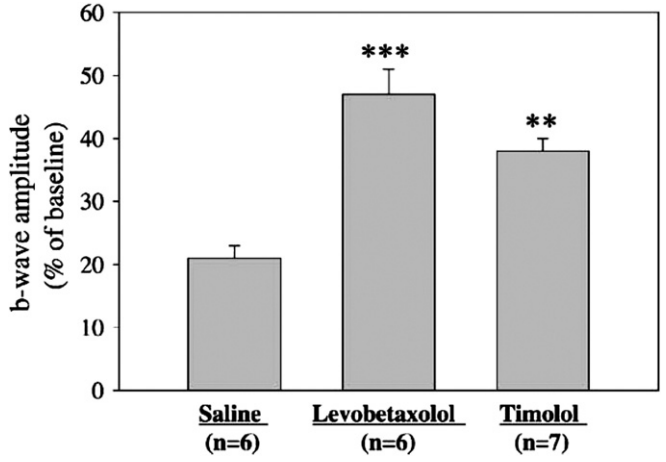

Fig. 12. Comparison of topically applied timolol and levobetaxolol as neuroprotectants. One drop of saline, 0.5% timolol (Martindale Pharmaceuticals) or 0.5% levobetaxolol (Alcon) was applied to both eyes, twice daily, to three groups of male Wistar rats for 5 days, at which point the intraocular pressure in one eye was elevated to 110 mmHg for 45 min. Saline or drug treatment continued for a further 5 days at which point the scotopic flash electroretinograms were recorded. The b-wave amplitude in the betaxolol-treated group is significantly greater than the saline-treated group (***$P < 0.001$). The b-wave amplitude in the timolol-treated group is also significantly greater than the saline controls (**$P < 0.01$) (one-way ANOVA and post hoc Tukey HSD). *Reprinted with permission from Brain Research from reference* (Osborne et al., 2004).

6. Conclusions

Glaucoma therapy has traditionally been focused on IOP reduction, as IOP reduction is known for a long time to slow down the progression of glaucomatous damage. This is evidence-based from large treatment controlled studies such as AGIS, OHTS and EMGT (Heijl et al., 2002, Higginbotham et al., 2004, Kass et al., 2002, Leske et al., 2007). There is even a kind of dose–response relationship: the lower the IOP, the lower the risk for progression. Therefore, the dogma "the greater the IOP reduction, the better the visual field prognosis" was formulated.

This exemplary comparison of two β-blockers, betaxolol and timolol, however, yielded a smaller rate of visual field deterioration in patients treated with betaxolol despite a lesser IOP reduction. The dissociation between IOP reduction and visual field prognosis reassessed here, postulates that not the amount of IOP reduction alone is relevant for successful treatment in glaucoma but also the drug by which the reduction is achieved. Direct drug-related effects on the vascular tone and thus OBF as well as on retinal ganglion cell survival may have a hitherto often underestimated effect on visual field prognosis.

7. Future directions

Ocular hypotensive drugs should be evaluated for their effects on visual field and not just on their potential capacity of IOP reduction. The data from this article imperatively highlights that not the target level of IOP alone is relevant in glaucoma treatment but also the drug by which this level is achieved. This is particularly important when comparing the efficacy of different drug classes among each other, e.g. an interclass comparison between prostaglandin analogues and beta-blockers. We urgently need more information about the genuine impact of drugs on visual field function, since visual function counts for the quality of life of our patients and not IOP.

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