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Perspective

New Approaches to Antiglaucoma Therapy

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Introduction

A detailed review on the pharmacology of antiglaucoma drugs was published in 1989[1] that discussed factors regulating intraocular pressure (IOP), the physiology of aqueous humor inflow and outflow, and drug delivery to the eye following topical dosing. Accordingly, these topics will not be covered in this review. In addition, references are essentially limited to those of the 1990s.

Chronic primary open-angle glaucoma is by far the most prevalent form of glaucoma. It is 7 times more prevalent in the United States than angle-closure glaucoma,[2] and in this review chronic open-angle glaucoma will be referred to as glaucoma. It has been estimated that the number of people in the world with glaucoma will approach 66.8 million by the year 2000 with fewer than 50% of those in developed countries being aware of their disease.[3] Glaucoma is the second most common form of blindness in the United States[4] and is much more prevalent in Afro-American than in Caucasian populations with age and IOP being the strongest risk factors across all population groups. Other risk factors include diabetes, systemic hypertension, severe myopia, and a family history of glaucoma.[5] An elevated IOP was formerly synonymous with glaucoma, but this is no longer the case as recent data have shown about one-sixth of patients with glaucoma have a "normal" IOP, e.g., less than 22 mmHg.[4] Glaucoma is best defined as an optic neuropathy with characteristic optic nerve head and associated visual field changes.[6] While the etiology of glaucoma remains unknown, two mechanisms have been proposed to explain the damage to the optic nerve in glaucoma, one mechanical and one vascular. The former suggests that distortion and displacement of the *lamina cribrosa* in the optic nerve results in axonal damage with ensuing blockade of axonal transport followed by axonal death. The vascular theory proposes that ischemia is responsible for axonal loss.[4] However, with recent biochemical and genetic studies, discussed at the end of the review, it is possible that other etiologies may exist for glaucoma. For example, it is distinctly feasible that even primary open-angle glaucoma could be more than one disease.

Glaucoma is a chronic disease lacking a cure and, if left untreated, continues to progress. Consequently, treatment should be commenced as soon after diagnosis as possible. At this point in time, the only high risk factor in glaucoma which can be modified is IOP, which is regulated by the rate at which aqueous humor is secreted and eliminated from the eye. The increase in IOP associated with glaucoma is due to an increased resistance to the outflow of aqueous humor from the eye through the trabecular meshwork—Schlemm's canal system.[1]

All drugs in current use to treat glaucoma are ocular hypotensive agents. The treatment of glaucoma was revolutionized in the late 1970s with the introduction of topical β-adrenoceptor antagonists. Following a dearth of new agents, the armamentarium of the physician has been recently enhanced with the launching of two α_2-adrenoceptor agonists, a topical carbonic anhydrase (CA) inhibitor and two prostaglandin agonists. Progress in the quest for new and novel ocular hypotensive agents will remain frontline therapy in the treatment of glaucoma for the foreseeable future. Other areas of current interest include low-tension glaucoma and neuroprotection.

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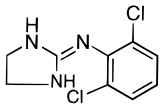
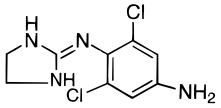
α_2-Adrenoceptor Agonists

Autoradiographic studies have shown that α_2-adrenoceptors are localized in the rabbit ciliary process,[7] the site of aqueous humor secretion, and in the human eye with high levels being detected in both the iris epithelium and ciliary epithelium with lower levels in the ciliary muscle and retina.[8] Ocular α_2-adrenoceptors are heterogeneous in nature. Pre- and postjunctional α_2-adrenoceptors are pharmacologically distinct as demonstrated by the use of the α_2-adrenoceptor antagonists, rauwolscine and SKF-104078, in ocular pre- and postjunctional assay systems.[9] There are currently at least four distinct α_2-adrenoceptor subtypes termed α_2A, α_2B, α_2C, and α_2D.[10] In the human ciliary body, α_2B and α_2C subtypes are present in the nonpigmented epithelium and ciliary muscle. In contrast, α_2A immunoreactivity is also present in the rabbit ciliary body.[11]

Topically applied clonidine has been used as an ocular hypotensive agent for over 20 years, but it has gained very little clinical acceptance due to its cardiovascular side effects.[12]



Clonidine



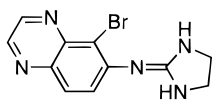
Apraclonidine

Apraclonidine is more polar than clonidine and was designed in an attempt to reduce the centrally mediated cardiovascular side effects of the latter. A 1% solution of apraclonidine was initially introduced clinically to control or prevent elevations in IOP that occur in patients after a number of surgical procedures.[13] A 0.5% solution was subsequently introduced with recommended three times a day short-term use in patients on maximally tolerated medical therapy who require an additional reduction in IOP.

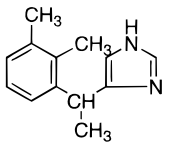
The administration of two drops of 0.5% apraclonidine to human volunteers resulted in a reduction in IOP. No contralateral effect on IOP was observed, indicating that the site of action was local within the eye, and changes in blood pressure and heart rate were absent.[14] In short-term studies up to 22 days, 1% apraclonidine produced a significant additional reduction in IOP when used as an adjunct to timolol.[15] In a 90-day study, 0.5% apraclonidine was found to be as equally effective as 1% apraclonidine when added to timolol therapy.[16] However, in a study in which 0.5% apraclonidine was used two or three times daily as monotherapy, tachyphylaxis was observed with approximately one-third of patients having to stop taking the drug because of failure to adequately lower IOP.[17] In addition, an ocular allergic reaction was detected in approximately 20% of patients. This has also been observed by others with the incidence reaching 48% in one study.[18]

The acute instillation of 1% apraclonidine was observed to decrease aqueous humor flow in human volunteers.[19] Others have reported that the twice daily instillation of 0.5% apraclonidine to ocular hypertensives resulted in increased trabecular outflow facility and a decrease in both aqueous flow and episcleral venous pressure.[20]

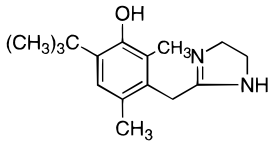
Brimonidine (UK-14304) is another α_2-adrenoceptor agonist[21] approved by the FDA for the treatment of glaucoma and ocular hypertension in September, 1996. The acute instillation of 0.2% brimonidine in healthy human volunteers elicited a reduction in IOP at peak similar to that seen with timolol. A slight reduction in systolic blood pressure during recovery from exercise and at 4 h after instillation were also reported.[22] The twice daily instillation of 0.2% brimonidine for 1 week to ocular hypertensives was associated with a decrease in aqueous humor flow and an increase in uveoscleral outflow, and in this respect appears to differ from apraclonidine.[23]



Brimonidine



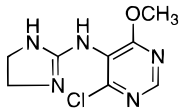
Medetomidine



Oxymetazoline

Other α_2-adrenoceptor agonists that have been shown in preclinical studies to have topical ocular hypotensive activity include medetomidine,[24] the D-enantiomer of which is the active entity[25] and which also lowered IOP in rabbits.[26] Oxymetazoline, which is present in over-the-counter nasal and ocular decongestants, has also been shown to be topically active.[27]

There are two subtypes of imidazoline recognition sites, termed I_1 and I_2, that are selectively labeled by [^{3}H]clonidine and [^{3}H]idazoxan, respectively.[28] Moxonidine is claimed to be selective for the I_1-imidazoline site[29] and has been observed to lower the IOP of rabbits following topical administration by reducing aqueous humor inflow, an effect mediated by an action on both imidazoline and α_2-adrenoceptors.[30] In contrast, the ocular hypotensive effect of brimonidine is primarily via α_2-adrenoceptors.[31]

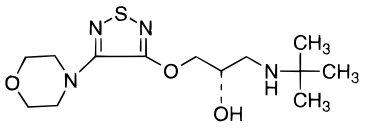


Moxonidine

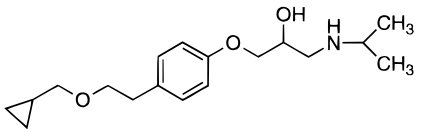
β-Adrenoceptor Antagonists

Topically applied β-adrenoceptor antagonists, e.g., timolol, betaxolol, levobunolol, metipranolol, and carteolol, have become the drugs of choice in the management of ocular hypertension and glaucoma.[32] All five drugs are β-adrenoceptor antagonists, but differences exist in their pharmacological profiles. Timolol, levobunolol, and metipranolol are nonselective β-adrenoceptor antagonists, whereas betaxolol displays selectivity for β_1- over β_2-adrenoceptors and carteolol possesses intrinsic sympathomimetic activity. These differences can have a bearing on the clinical profiles of the drugs.

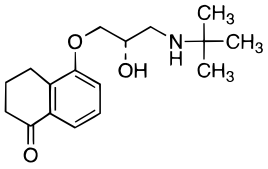
All five drugs are generally well tolerated following topical administration, although metipranolol has been associated with more ocular burning, stinging, and granulomatous anterior uveitis than the other agents.[33] All lower IOP by decreasing the production of aqueous



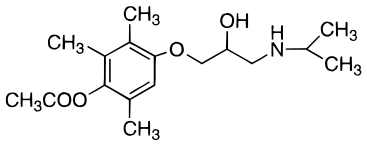
Timolol



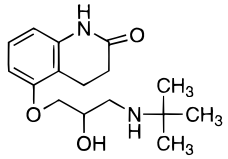
Betaxolol



Levobunolol



Metipranolol

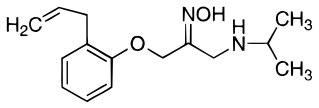


Carteolol

humor.[34] In terms of ocular hypotensive efficacy, betaxolol may be somewhat less effective.[35] Although these drugs are applied topically, they may enter the general circulation and reach concentrations high enough to elicit systemic effects, e.g., alterations in heart rate and rhythm, bronchoconstriction, dyslipidemia, and central nervous system abnormalities.[34] Perhaps the most serious of these are the respiratory side effects.[35] These side effects can occur not only in patients known to be susceptible but also in patients without a prior history of respiratory problems.[36] Respiratory side effects are less with betaxolol than with nonselective β-adrenoceptor antagonists as would be predicted on the basis of its weaker affinity for the β_2-adrenoceptor. However, this drug is not free of the potential of respiratory problems.[34,35] The intrinsic sympathomimetic activity of carteolol has yet to display a distinct advantage over the other agents in terms of side effects.[33,34]

A β-adrenoceptor antagonist possessing the ocular hypotensive efficacy of nonselective β-adrenoceptor antagonists but devoid of systemic side effects would represent a major breakthrough in therapy. Attempts have been made to achieve this using a variety of approaches. An obvious goal is to minimize the amount of drug in the systemic circulation following topical dosing. The simplest method of achieving this is by keeping the eye closed after dosing and also by applying fingertip pressure to the inner corner of the eye to occlude the nasolacrimal drainage system. In the case of timolol, this has resulted in an improved therapeutic index due to lower dosing and less frequent administration being required while still maintaining ocular hypotensive activity.[37] An alternative strategy is modifying the formulation of the drug as has been done with timolol. The frequency of dosing with timolol has been reduced from twice daily to once daily by incorporating the drug in a gellan gum vehicle (Gelrite),[38] an anionic heteropolysaccharide that forms a clear gel in the presence of cations.[39] The Na^+ concentration in tears is sufficient to cause gelation of the solution when topically administered. Reductions in the heart rate of healthy volunteers both at rest and after exercise were less after once daily 0.5% timolol in gellan gum than after twice daily timolol solution.[40]

Two synthetic approaches have been used to improve the therapeutic index of β-adrenoceptor antagonists. The first of these is a site-specific chemical delivery system. This approach involves designing an inactive chemical precursor of an active drug, which is then activated within, and only within the eye.[41] Using this concept, ketoximes corresponding to β-adrenoceptor antagonists including timolol, propranolol, and carteolol were synthesized. Of the compounds tested, propanolol oxime was the most potent in lowering the IOP of rabbits.[42] These studies were extended to alprenolone oxime (alprenoxime), the oxime analog of alprenolol, and this

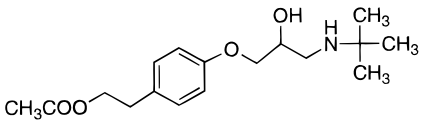


Alprenoxime

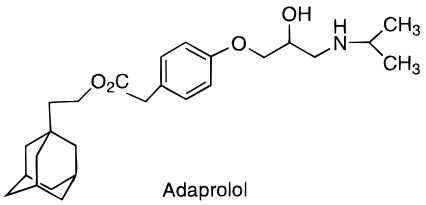
agent displayed good ocular hypotensive activity in rabbits.[43] In contrast, little effect was seen on the cardiovascular system of both animals[44] and humans.[45] However, pharmaceutical instability precluded the further development of the compound.[45] In an attempt to overcome this lack of stability and ocular irritation in rabbits, alprenolol methoxime was synthesized. This compound elicited a prolonged reduction in the IOP of rabbits following topical dosing. In addition, it was stable in solution and nonirritant to the rabbit eye.[46] The concept has also been applied to betaxolol, and its oxime analog was also effective in decreasing the IOP of rabbits.[45]

The second avenue to improve the therapeutic index of β-adrenoceptor antagonists is the "soft drug" approach which produces their pharmacological effect locally but their distribution away from the site will result in prompt metabolic deactivation with a resultant loss in pharmacological activity. This has been done using metoprolol. The major metabolite of metoprolol is the phenylacetic acid derivative which loses activity, but its esterification restores β-adrenoceptor blocking activity. Of the various lipophilic esters of the phenylacetic acid derivative of metoprolol prepared, the most interesting was the admantane ethyl ester which lowered the IOP of rabbits and was nonirritant.[47] The soft drug approach was also used for L-653,328, the acetate ester of L-652,698. Topically applied L-653,328 decreased the IOP of ocular normotensive and hypertensive rabbits. In contrast to timolol, L-653,328 was unable to block isoproterenol-induced changes in the blood pressure and heart rate of rabbits following topical dosing.[48] The acute instillation of 2% L-653,328 to human volunteers resulted in a reduction in IOP which was less than the elicited by 0.5% timolol. However, in contrast to timolol, there was no evidence of systemic β-adrenoceptor blockade.[49] In a follow-up study, it was observed that cumulative concentrations of L-653,328 up to 4% did not cause bronchoconstriction in asthmatic patients.[50] An-

other example of the soft drug approach is adaprolol, a compound that can be chemically viewed as the adamantane ethyl ester of an inactive carboxylic acid metabolite of both atenolol and metoprolol. Topically applied (*R*)-(−)-adaprolol was equally effective as racemic adaprolol and its (*S*)-(+)-enantiomer in lowering the IOP of rabbits. However, in contrast to its (*S*)-(+)-enantiomer, (*R*)-(−)-adaprolol possessed negligible systemic β-adrenoceptor blocking activity.[51]



L-653,328



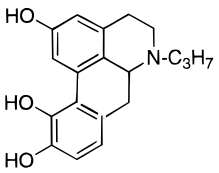
Adaprolol

A topically effective, ocular hypotensive β-adrenoceptor antagonist lacking systemic side effects would undoubtedly be a major advance in glaucoma therapy.

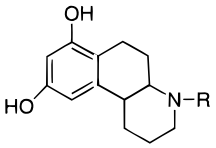
Dopaminergic Agonists

While autoradiographic studies to localize D_1 and D_2 receptors in the anterior portion of the rabbit eye were unsuccessful,[52] the incubation of the trabecular meshwork of porcine and canine eyes in the presence of the D_1 receptor agonist, fenoldopam, resulted in an increase in c-AMP content, indicating the presence of functional D_1 receptors in the tissue.[53] High-affinity binding sites for the D_1 receptor antagonist, SCH 23390, are present in the bovine ciliary body. In contrast, specific D_2 binding sites were not observed.[54] Others have also demonstrated by light microscope autoradiography that D_1 receptor sites are present within the epithelium of the rabbit ciliary process whereas none were detected in the outflow pathway.[55] While dopamine had no effect, the ability of forskolin to increase c-AMP levels in human nonpigmented ciliary epithelial cells can be enhanced by the addition of dopamine, leading to the suggestion that the effect of dopamine on adenylate cyclase activity is mediated by β-adrenoceptor activation and not to D_1 receptors.[56]

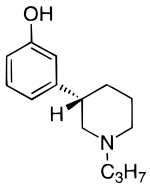
In spite of the failure to demonstrate the presence of D_2 receptors in the anterior portion of the eye, the topical administration of agonists for this receptor subtype is associated with a reduction in IOP. For example, dosing with 25−250 μg of the D_2 receptor agonist, 2,10,11-trihydroxy-*N*-*n*-propylnoraporphine (TNPA), lowered the IOP of rabbits. Unilateral instillation elicited a contralateral effect. The decrease in IOP was mediated by diminished aqueous humor inflow. This effect of TNPA was absent in surgically sympathectomized rabbit eyes. In a test for prejunctional activity, TNPA inhibited the release of [^{3}H]norepinephrine from the isolated, field-stimulated iris-ciliary body of the rabbit. In a test for postjunctional activity, isoproterenol-induced stimulation of c-AMP accumulation in the isolated rabbit ciliary body was unaltered by TNPA. The outcome of these findings is that the ocular hypotensive effect of TNPA is exerted predominantly on prejunctional D_2 receptors of peripheral sympathetic nerves to inhibit the release of norepinephrine.[57] The octahydrobenzo[*f*]quinolines, Ha117[58] and Ha118,[59] have a similar pharmacological profile. The (*S*)-enantiomer of 3-PPP (3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine) is a partial agonist at dopamine autoreceptors and the IOP of rabbits is lowered following its topical administration.[60] In a follow-up study, the combination of (*S*)-(−)-3-PPP and the phosphodiesterase inhibitor, pentoxifylline, resulted in enhanced ocular hypotensive activity. Interestingly, the dopamine receptor antagonist, trifluperidol, displayed a similar profile.[61] The acute instillation of 0.1% SDZ GLC-756, a D_2 agonist/D_1 antagonist, lowers the IOP of both normal volunteers and glaucoma patients. A contralateral effect was present, but no ocular or systemic side effects, except for transient hyperemia, were observed.[62]



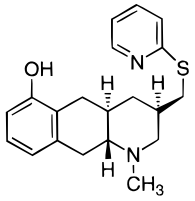
TNPA



Ha117 R=C_3H_7
Ha118 R = C_2H_5



(S)-PPP



SDZ GLC-756

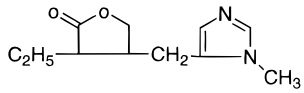
D_2 agonists, by decreasing the release of norepinephrine in the eye, can be functionally viewed as indirectly acting β-adrenoceptor antagonists, and it is difficult to envisage any major improvement in efficacy over the latter class of agents at the present time.

Cholinergic Agonists

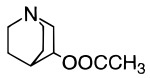
Pilocarpine and epinephrine are the oldest drugs used to treat glaucoma. Pilocarpine lowers IOP by increasing conventional aqueous humor outflow through the trabecular meshwork by contracting the ciliary muscle which, in turn, physically alters the configuration of the trabecular meshwork leading to an increased free flow of aqueous humor. The major side effects associated with pilocarpine are cycloplegia, i.e., loss of accommodation, and miosis, i.e., pupillary constriction, and are the result of the drug activating muscarinic receptors in the ciliary muscle and iris, respectively.[1]

Four pharmacologically distinct muscarinic receptors, M_1, M_2, M_3, and M_4, have been characterized, and five human muscarinic receptors, i.e., m_{1-5}, have been cloned and expressed. The M_1, M_2, and M_3 receptors correspond to the m_1, m_2, and m_3 receptors, respectively.[63]

Pilocarpine is nonselective for muscarinic receptor subtypes.[64,65] The hypothetical situation that ocular hypotension, on one hand, and cycloplegia and miosis,



Pilocarpine



Aceclidine

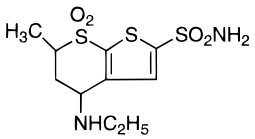
on the other, are mediated by different muscarinic receptors is an attractive concept and, if correct, could result in novel ocular hypotensive agents. There is some evidence to support this concept. Aceclidine, a muscarinic agonist marketed in Europe, markedly increased outflow facility in monkeys but had little effect on accommodation compared to pilocarpine following intracameral injection, i.e., into the anterior aqueous fluid. However, miotic activity was retained.[66] The functional agonist activity of aceclidine was also higher in the trabecular meshwork than in the ciliary muscle of the cow.[67]

Characterization of muscarinic receptor subtypes in ocular tissues has also shown that the M_3 is the predominant subtype present in both the iris and ciliary muscle of animals[68] and humans[69] and in the human trabecular meshwork.[69,70] Attempts to dissociate the accommodative, outflow facility and miotic responses to aceclidine in the rhesus monkey by the use of antagonists possessing varying degrees of selectivity for muscarinic receptor subtypes were unsuccessful, the M_3 antagonist, 4-DAMP, being the most potent against all three responses.[71] Thus it would appear difficult to dissociate the ocular hypotensive effects of a cholinergic agonist from its side effects.

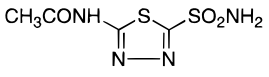
Other efforts to improve the pharmacological profile of pilocarpine have focused on prodrugs of pilocarpine[72] and modified pharmaceutical formulations.

Topical Carbonic Anhydrase Inhibitors

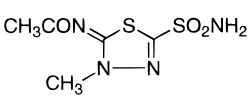
Dorzolamide is the first topical CA inhibitor to be used clinically for the treatment of ocular hypertension and/or open-angle glaucoma.[73] In contrast to oral CA inhibitors, such as acetazolamide and methazolamide, dorzolamide has good aqueous solubility and this, together with its lipophilicity, accounts, in part, for its topical activity. The compound is used either as monotherapy or as adjunctive therapy to other ocular hypotensive agents. The drug was introduced in the United States and several other countries in 1995.[73]



Dorzolamide



Acetazolamide



Methazolamide

There are at least seven different isoenzymes of CA[74] and, of these, isoenzymes I and II, and possibly IV, are important in the overall pharmacology of dorzolamide. The cytosolic CA-II isoenzyme has traditionally been viewed as critical in the formation of aqueous humor. However, there is currently considerable speculation on the significance of membrane bound CA-IV.[75] An argument against a role for CA-IV in humans is the failure to detect its presence in the ciliary process.[76] In addition, orally administered acetazolamide was unable to lower the IOP of individuals deficient in CA-II.[77] Dorzolamide is a potent inhibitor *in vitro* of human CA-II and CA-IV but unlike acetazolamide and methazolamide is a very weak inhibitor of human CA-I.[73] This point is important in the overall pharmacology of dorzolamide because approximately 90% of CA in the human red blood cell is CA-I.[78] Hence, the propensity of dorzolamide for the total inhibition of red blood cell CA-I is less than that of acetazolamide or methazolamide. Dorzolamide fits very well into the active site of CA-II, and three-dimensional X-ray crystallography has revealed that its ethylamino group changes the position of histidine-64 in the active site of the enzyme with the result that water can no longer be bound.[79] In addition to being a potent inhibitor of CA, dorzolamide is a good ocular penetrator following topical dosing,[80] and it is the combination of these properties which accounts for its ocular efficacy.

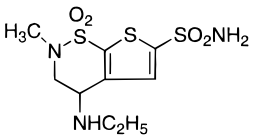
Early clinical studies in the development of dorzolamide have been reviewed.[81] In a one-year study comparing the ocular hypotensive effects of 2% dorzolamide administered three times daily, 0.5% betaxolol twice daily, and 0.5% timolol twice daily, peak IOP reductions of 23%, 25%, and 21% were observed, respectively. Tachyphylaxis did not develop to dorzolamide, nor were electrolyte and/or systemic side effects encountered.[82] The latter is consistent with a study in humans in which plasma levels of dorzolamide were lower than the limit of detection of the assay (5 ng/mL) at a time when the red blood cell content of dorzolamide had reached steady state which was appreciably less than the red blood cell content of the enzyme.[83] Patients taking 0.5% timolol twice daily received either 2% dorzolamide twice daily or 2% pilocarpine four times daily for 6 months, and the additional reductions in IOP elicited by dorzolamide and pilocarpine were very similar. However, pilocarpine usage resulted in a higher discontinuation rate.[84] In a separate study in which dorzolamide and pilocarpine were compared at these dosage schedules, patients preferred dorzolamide to pilocarpine by a ratio of >7:1 in terms of quality of life measures.[85] The acute administration of 2% dorzolamide to human volunteers has been observed to increase retinal blood flow velocity.[86] In common with orally administered CA inhibitors, topically administered dorzolamide has been observed to reduce aqueous humor production in rabbits,[73] monkeys,[87] and humans.[88]

Other topically applied CA inhibitors in preclinical evaluation are thiophenes, e.g., AL-4414A,[89] thiadiazole analogs (**1**, **2**),[90,91] and sulfamates, e.g., AHR-16329.[92] Topically applied acetazolamide does not lower rabbit IOP, but its instillation in (2-hydroxypropyl)-β-cyclodextrin was effective.[93]

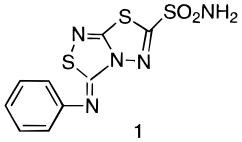
Prostaglandin Agonists

On the basis of isolated tissue and platelet studies, five types of PG receptors were proposed based on their affinity for the naturally occurring PGs, i.e., PGE_2 (EP), $PGF_{2\alpha}$ (FP), PGD_2 (DP), thromboxane (TP), and prostacyclin (IP).[94] The EP receptor has been further classified into four subtypes EP_1-EP_4.[95]

Binding sites selective for PGE_2 have been identified in the bovine iris−ciliary body.[96] In a follow-up study, in which the regional distribution and selectivity of PGE_2 and $PGF_{2\alpha}$ specific binding sites in membrane



AL-4414A



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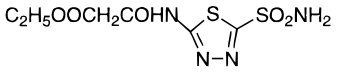

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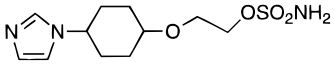
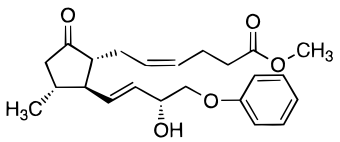


AHR - 16329

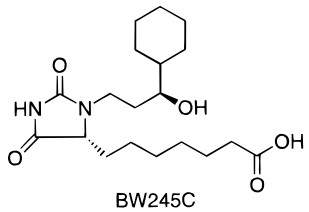
preparations of the bovine sphincter, ciliary body, and remaining iris tissue were studied, the majority of the PGE_2 specific binding sites were in the sphincter muscle (65%), followed by the iris (17%) and ciliary body (18%). $PGF_{2\alpha}$ binding sites were not measurable in either the iris or the ciliary muscle, and binding in the sphincter muscle was primarily to EP_2 receptors.[97] Also in the rabbit the predominant binding site in the iris−ciliary body was the EP_2 subtype with more binding sites being present in the ciliary body than in the iris and sphincter muscle.[98] The highest expression of FP receptor mRNA and protein in the cynomolgus monkey eye was found in the corneal, conjunctival and irideal epithelium, the ciliary muscle, and ciliary processes. Overall, the results indicated a low abundance of FP receptor transcripts and protein.[99] Binding sites for $PGF_{2\alpha}$ and PGE_2 have been localized in human eye sections using autoradiography. Specific binding sites for both PGs were co-localized at a high level in areas of the ciliary muscle and the iris sphincter muscle, and at a lower level in the iris epithelium and the retina. The binding of $PGF_{2\alpha}$ was totally displaced by PGE_2 whereas the binding of PGE_2 was not totally displaced by $PGF_{2\alpha}$.[100] These experiments were extended to include competitive displacement studies, with the radioligands being PGD_2, PGE_2, and $PGF_{2\alpha}$. The results indicated that the predominant PG receptor in the human ciliary muscle was the EP_2 subclass and that there was a small number of DP receptors. Few, if any, FP receptors appeared to be present.[101] Sympathetic nerves in the human iris−ciliary body possess prejunctional inhibitory PG receptors that have the pharmacological properties of the EP_3 subtype.[102]

PG receptors have different second messenger systems. EP_1 and FP receptors stimulate phosphoinositidase C, whereas EP_2, DP, and IP receptors stimulate adenylate cyclase. EP_3 receptor activation can block adenylate cyclase and stimulate phosphoinositidase C.[95] The ability of $PGF_{2\alpha}$ to stimulate the accumulation of inositol triphosphate (IP_3) in the iris sphincter muscle is species dependent with low functional activity in the rabbit and human,[103] suggesting a minor role for the FP receptor in the human and rabbit iris sphincter. The IP_3 response of the bovine iris sphincter muscle to $PGF_{2\alpha}$, a functional indication of the presence of the FP receptor, is at variance with the binding study cited above which failed to demonstrate binding sites for $PGF_{2\alpha}$ in the bovine iris−ciliary body. To further complicate the picture, phosphoinositidase C activity in the iris−ciliary body of the rabbit has been reported to be stimulated by agonists for either the EP_1 or the FP receptor.[104] The stimulation of adenylate cyclase activity in the iris−ciliary body of the rabbit has been observed to be predominantly mediated by the EP_2 receptor, and such a predominance of the EP_2 receptor was not observed in the cat and cow.[105]

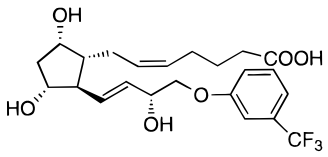
An alternative strategy for exploring the role of prostaglandins in the eye has been to administer topically agents possessing some degree of agonist selectivity for PG receptor subtypes and recording subsequent changes in IOP. Application of five $PGF_{2\alpha}$ analogs to the eyes of cats and rabbits showed that their ability to lower IOP could not be correlated with their affinities for the FP receptor.[106] However, EP_3 but not EP_2, FP, or TP receptor activation was correlated with ocular hypotensive effects in rabbits.[107] RS-61565, a potent EP_3 receptor agonist, had good IOP-lowering activity with no signs of ocular irritation in this study. In contrast, conjunctival hyperemia and little change



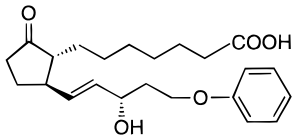
RS-61565



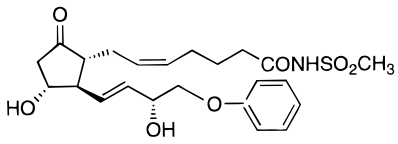
BW245C



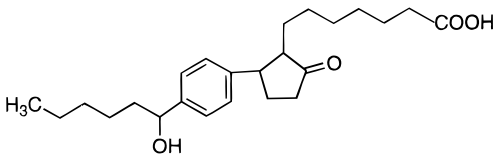
Fluprostenol



MB 28767



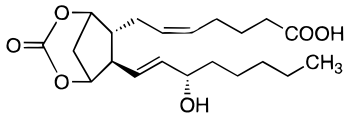
Sulprostone



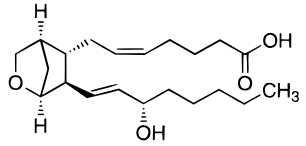
AH 13205

in IOP were observed in human volunteers following its acute topical administration.[108] While the EP_3 receptor appears to be involved in reducing IOP in rabbits, there is evidence to indicate that the breakdown of the blood−aqueous barrier in rabbits by prostaglandins involves the EP_2 receptor.[109] Another example of discordant findings between rabbits and humans is provided by the PGD_2 analog, BW 245C. Its topical administration to rabbits resulted in a decline in IOP and an absence of ocular irritation.[110] In contrast, BW 245C was irritant and weakly active in humans.[111] It has been observed that the IOP of both dogs and monkeys was decreased to varying degrees following the instillation of the FP agonists, fluprostenol and 17-phenyl $PGF_{2\alpha}$, the EP_3 agonists, MB-28767 and sulprostone, and an EP_2 agonist, 11-deoxy PGE_1. The ability of both 17-phenyl $PGF_{2\alpha}$ and MB-28767 to lower monkey IOP was enhanced following their twice daily instillation for five days. In contrast, the ocular hypotensive response to twice daily 11-deoxy PGE_1 was transient.[112] Topical dosing with another EP_2 agonist, AH 13205, lowered the IOP of ocular normotensive and hypertensive monkeys although its effect was less than that of EP_3 and FP agonists.[113]

Thromboxane A_2 receptors are concentrated on nonpigmented epithelial cells of the ciliary process, on photoreceptors within the retina, and on endothelial cells of the posterior ciliary arteries in humans.[114] Studies in dogs and monkeys indicate the existence of heterogeneous populations of TP receptors in the eye as indicated by the ability of the thromboxane A_2 agonists, AGN 191976 and U-46619, to lower and leave unchanged the IOP of both species, respectively. In contrast, both agents increased conjunctival vascular permeability.[115]



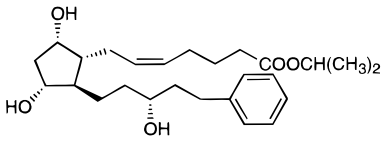
AGN 191976



U-46619

The topical administration of $PGF_{2\alpha}$ isopropyl ester lowered the IOP of glaucoma patients.[116] However, conjunctival hyperemia was also observed, and this, together with ocular irritation and foreign body sensation, prevented further clinical use. Attempts to reduce these side effects by a prodrug approach through the esterification of different parts of the molecule were unsuccessful.[117,118] A series of $PGF_{2\alpha}$ acyl esters comprising 11-mono-, 15-mono-, and 11,15-diesters retained ocular hypotensive activity in rabbits, and a temporal dissociation between the reduction in IOP and hyperemia was seen, especially at extended time points.[119]

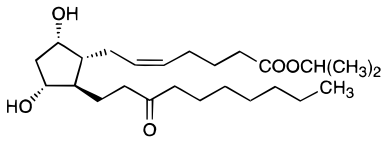
The substitution of part of the ω side chain of analogs of $PGF_{2\alpha}$ with a phenyl ring resulted in compounds with a reduced propensity for hyperemia while retaining IOP-lowering activity.[120] These phenyl-substituted esters penetrated the cornea *in vitro* and were hydrolyzed to their corresponding acids.[121] Hyperemia and ocular irritation were assessed in cats and rabbits, respectively, whereas measurements of IOP were made in ocular normotensive monkeys.[122] The most interesting compound to emerge was PhXA34 which, like the FP agonists, fluprostenol and 17-phenyl $PGF_{2\alpha}$, failed to lower the IOP of cats and rabbits. The repeated twice daily instillation of 0.003% or 0.01% solutions of PhXA34 lowered the IOP of patients with ocular hypertension.[123] The 15*R* epimer of PhXA34 is latanoprost (PhXA41), which was efficacious in patients with increased IOP following twice daily dosing.[124] It was subsequently found that this dosage schedule could be reduced to once daily administration.[125] The ocular hypotensive effect of timolol was enhanced by the once daily concomitant administration of latanoprost.[126] The once daily instil-



Latanoprost

lation of 0.005% latanoprost was associated with a retention of ocular hypotensive activity for 6 months. However, an unusual side effect was an increase in irideal pigmentation, particularly in individuals with green-brown or blue-brown eyes. This phenomenon is thought to be due to an increased synthesis of melanin by irideal melanocytes and does not appear to be reversible.[127,128] Whether this phenomenon is of minor or major clinical significance will depend upon the outcome of long-term studies. The ocular hypotensive effect of latanoprost in humans has been demonstrated to be due to an increase in uveoscleral outflow.[129,130] The increased porosity of the ciliary muscle is possibly the result of stimulation of collagenase or other matrix metalloproteinases that alter the extracellular matrix.[131] Uveoscleral outflow is generally viewed as contributing 5−20% of the total drainage of aqueous humor from the human eye.[132] Hence, its contribution under normal physiological conditions is appreciably less than that of trabecular outflow. Latanoprost was approved by the FDA in June 1996.

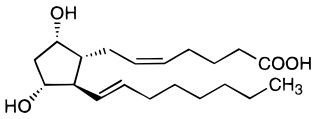
Unoprostone (UF-021) is a 22-carbon chain derivative of a metabolite of $PGF_{2\alpha}$ that is marketed in Japan. The twice daily instillation of 0.12% unoprostone has been observed to maintain IOP lowering activity for 12 weeks.[133] Unoprostone, like latanoprost, is thought to produce its ocular hypotensive effect by increasing uveoscleral outflow.[134]



Unoprostone

The twice daily instillation of a 0.3% solution of the PG analog, S-1033, to healthy human volunteers showed a sustained ocular hypotensive effect in an 8-day study.[135] The ability of S-1033 to lower the IOP of

anesthetized cats has been observed to be due to an increase in conventional aqueous humor outflow,[136] indicating that all PGs may not share the same mechanism of action, namely increased uveoscleral outflow.



S-1033

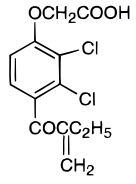
Latanoprost has a high affinity for the FP receptor, being approximately half that of $PGF_{2\alpha}$. In contrast, its affinity for EP_1, EP_2, EP_3, DP, IP, and TP receptors is low.[122] S-1033 was also selective for the FP receptor while unoprostone had a weak affinity for all PG receptors.[137]

Prostaglandin agonists represent novel and exciting ocular hypotensive agents. However, they are not free of ocular side effects, and their mechanism of action is not a major contributor in the physiological regulation of aqueous humor inflow and outflow. Their overall importance will be dependent on the outcome of further long-term studies.

Directly Acting Conventional Outflow Enhancers

Epinephrine can enhance aqueous humor outflow in the human eye.[1] However, epinephrine possesses a myriad of side effects, and its clinical use is limited to add-on therapy in patients for whom β-adrenoceptor antagonists are contraindicated. Consequently there is clearly a need for ocular hypotensive agents that directly increase conventional aqueous humor outflow.

Ethacrynic acid (EA; 0.4 mM) is one such entity that produces a change in the cell shape of cultured human and bovine trabecular meshwork cells that was coincident with a change in the staining pattern of major cytoskeletal components including actin, α-actinin, vinculin, and vimentin. This effect is though to be a



Ethacrynic Acid

sulfhydryl-reactive mechanism.[138] The perfusion of anterior segments of human donor eyes with EA (0.01−0.25 mM) resulted in outflow facility being increased from 28% to 105%, a finding consistent with the cytoskeletal changes in outflow pathway cells described above. EA (0.25 mM) is, however, associated with some cell swelling and necrosis.[139] Single doses of EA ranging from 0.05 to 0.6 mM increased by at least 40% outflow facility of human eyes in perfusion organ culture that maintained the viability of the cornea and trabecular meshwork for up to 4 weeks. However, at concentrations of 0.1 mM and higher, EA elicited undesirable histological changes in trabecular cells, and no recovery or reversal was observed at 2 weeks after a single exposure to the drug.[140] Intracameral injection of EA (0.05−0.15 mM) into the eyes of patients with advanced glaucoma elicited a profound decline in IOP which lasted for up to 3 days. There was no evidence of corneal side effects.[141] Similar studies were conducted in monkeys, but an intracameral injection of 3 mM EA was required to provide a reliable reduction in IOP. At 3.75 mM, EA caused corneal edema.[142] Thiol adducts of EA were used as an approach to reduce corneal side effects, and EA−cysteine (0.25 mM) was very effective in increasing the outflow facility of perfused enucleated calf eyes.[143] This adduct possessed less ocular hypotensive activity in rabbits and monkeys than EA itself, and corneal toxicity was not eliminated.[144] The once daily topical administration of a 1.5% EA ointment to glaucomatous monkeys caused a reduction in IOP comparable to that of 0.5% timolol administered twice daily, but some ocular adverse effects were present.[145] A similar treatment with this formulation to ocular normotensive cynomolgus monkeys increased outflow facility by 40% on day five and lowered IOP by 13−26%. However, clinically unacceptable corneal toxicity was observed.[146]

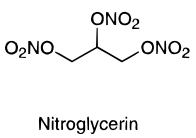
The view has been expressed that the ocular hypotensive effect of EA may not be due to an effect on trabecular meshwork actin filaments.[147] In addition to being a sulfhydryl-reactive drug, EA is also an inhibitor of the Na−K−Cl cotransporter in avian erythrocytes,[148] which is also present in human and bovine trabecular meshwork cells and is inhibited by EA. Drugs which lower or raise IOP were found to inhibit or stimulate the cotransporter, respectively. Inhibition of the cotransporter reduced the intracellular volume of trabecular meshwork cells whereas its stimulation increased cell volume. Hence, the Na−K−Cl cotransporter in trabecular meshwork cells may be of major importance in the regulation of intracellular volume and the permeability of these cells.[149] The significance of this system in the regulation of IOP clearly awaits resolution. More than one Na−K−Cl cotransporter exists and this topic has been reviewed in detail.[150]

Guanylate Cyclase Activators

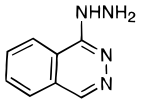
Convincing evidence is available to indicate that the elevation of ocular levels of c-GMP is associated with a reduction in IOP. The topical administration of the stable c-GMP analog, 8-bromo-cGMP, to rabbits resulted in a decrease in IOP that was not due to a change in outflow facility.[151] Its intravitreal injection decreased aqueous humor formation and increased outflow facility in monkeys.[152]

Atrial natriuretic peptide (ANF), an activator of guanylate cyclase, can lower the IOP of rabbits following its direct injection into the eye.[1] The ability of intravitreally administered ANF to elicit ocular hypotension in rabbits is associated with a decrease in aqueous humor production.[153] In contrast, intracamerally administered ANF increases uveoscleral outflow while reducing the IOP of cynomolgus monkeys.[154] The acute intravenous injection of ANF (100 μg) reduced the IOP of glaucoma patients for more than 8 h.[155] ANF is metabolically degraded by neutral endopeptidase, and inactivation of the latter can prolong the biological availability of ANF.[156] Oral dosing for 4 weeks with the neutral endopeptidase inhibitor, candoxatril, resulted in a reduction in the IOP of ocular normotensive individuals, an effect that was positively correlated with increases in plasma ANF levels and not with changes in systemic blood pressure.[157] Like ANF, nitrovasodi-

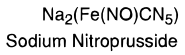
lators such as nitroglycerin stimulate guanylate cyclase via the production of nitric oxide, and the acute topical administration of agents such as nitroglycerin, hydralazine, and sodium nitroprusside can lower the IOP of rabbits, an effect associated with an increase in aqueous humor outflow. In contrast to chronic nitroglycerin, multiple dosing with hydrazaline did not elicit tachyphylaxis.[158] Hydrazaline has also been observed to increase aqueous humor outflow in monkeys.[159] However, nitroglycerin, at 0.1%, failed to lower the IOP of glaucomatous monkeys.[160]



Nitroglycerin



Hydralazine



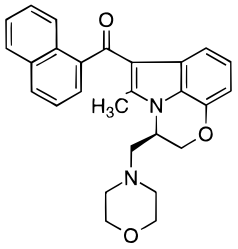
$Na_2(Fe(NO)CN_5)$
Sodium Nitroprusside

Although both atriopeptins and nitrovasodilators lower IOP, their physiological actions in the eye are not identical. As indicated above, ANF and nitrovasodilators decrease aqueous humor production and increase outflow facility in rabbits, respectively, reflecting differences in their target enzymes. The ANF-sensitive membrane bound and the nitrovasodilator-sensitive cytosolic guanylate cyclase are separate gene products, and their distribution in the eye is as yet unknown.[161] The effects of natriuretic peptides on c-GMP accumulation in cultured human trabecular meshwork and ciliary muscle cells is mediated via activation of the type B natriuretic peptide receptor.[162] Hydralazine has been evaluated at 0.03% and 0.1% in human volunteers, and no ocular hypotensive activity was observed.[163]

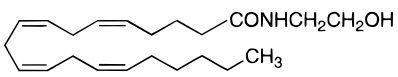
Soluble guanylate cyclase is also activated by nitric oxide (NO),[164] which is formed during the conversion of arginine to citrulline and involves nitric oxidase synthetase (NOS) of which three distinct mammalian isoenzymes have been cloned.[165] NOS-like immunoreactivity has been detected in the rat ciliary process.[166] The distribution of NADPH-diaphorase is highly correlated with that of NOS, and using this as a marker, NOS was observed to be present in the rabbit ciliary process.[167] In the human eye, both the ciliary muscle and the outflow pathway are substantially enriched sites of NOS.[168] In a study assessing anterior segments from normal and glaucomatous eyes, NOS-like reactivity was found to be decreased in the ciliary muscle, and in the trabecular meshwork and canal of Schlemm of patients with primary open-angle glaucoma. However, it is not known whether this is the cause of primary open-angle glaucoma or is the result of the disease.[169] The acute intracameral and intravitreal injection of the NO donors, 3-morpholinosyndnonimine and (*S*)-nitrosoacetylpenicillamine, decreased the IOP of rabbits,[170] suggesting an important role for NO in the regulation of IOP.

Cannabinoids

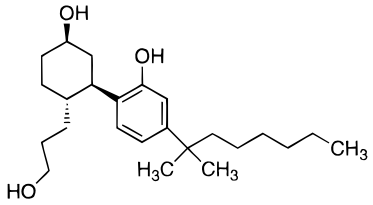
Cannabinoid (CB) receptor ligands like WIN 55,512-2 and CP 55,940 reduce rabbit and monkey IOP when given topically, showing enantiomeric selectivity.[171,172] WIN 55,512-2 decreased aqueous humor production in rabbits but had no effect on outflow in rabbits or monkeys.[173]



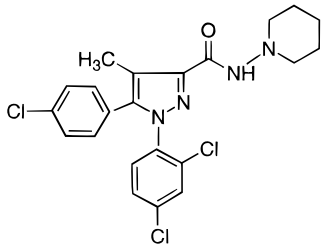
Win 55,212-2



Anandamide



CP 55,940



SR141716A

Research into cannabinoids as ocular hypotensive agents has been somewhat limited due to concerns related to the separation of the ocular hypotensive effects from the psychoactive properties of this class of compound. The discovery of cannabinoid receptor subtypes, both G-protein-coupled receptors, that show selective tissue distribution offers a means to delineate these properties.[174] The CB-1 receptor mediates the CNS effects of the cannabinoids while the CB-2 receptor is present in the spleen and other tissues.[175,176] Both cannabinoid receptors can be labeled with the synthetic ligand, [^{3}H]CP 55,940,[175] and the structure−activity relationship for binding affinity to this receptor correlated well with the analgesic actions of various cannabinoids.[171] The CB-1 receptor has been cloned,[177] and an endogenous ligand, anandamide[178] has been identified that can decrease IOP.[179] This effect is blocked by indomethacin, suggesting an involvement of prostaglandins in this effect.[180] A series of noncannabinoid ligands that include WIN 55,212-2,[181] CP 55,940,[172] and SR 141716A[182] have also been identified. WIN 55,512-2 is 19-fold more selective for the CB-2 receptor[183] while SR 141716A has nanomolar affinity for the CB-1 receptor with negligible activity at the CB-2 site.[182] SR 141716A apparently binds to the CB-1 receptor differently from WIN 55,512-2 as the latter compound shows 25-fold lower affinity for [^{3}H]SR 141716A binding than for [^{3}H]WIN 55,212-2 binding.[184] This may be related to a lysine at position 192 in the

third transmembrane domain of the human CB-1 receptor that is distinct for WIN 55,512-2 binding.[185]

Endothelin

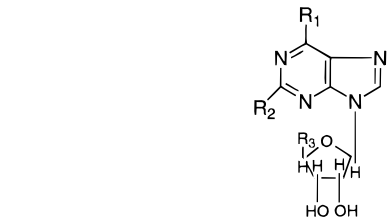
Endothelin (ET) was isolated and identified in 1988[186] and exists in three isoforms (ET-1, ET-2, and ET-3) with each having a separate gene.[187] In the rat iris, the levels of messenger RNA for endothelin are among the highest of any tissue.[188] Pronounced endothelin-like immunoreactivity has been observed in the human nonpigmented and pigmented epithelium at the crests of the pars plicata. This distribution of immunoreactivity in the human eye is similar to that of CA.[189] The distribution of ET-1 and ET-3 immunoreactivity has been studied in human, rat and porcine eyes. Highest amounts of ET-1 immunoreactivity in the human eye were present in the choroid and iris−ciliary body. The distribution of ET-3 immunoreactivity was similar to that of ET-1 except that there was generally 3 times as much ET-3 present. Distribution was not uniform for all three species.[190] High levels of ET-1 and ET-3 have also been observed to be present in the rabbit iris−ciliary body.[191] There are at least two distinct types of endothelin receptors. ET_A is selective for ET-1 and ET_B is equally sensitive to all ET isopeptides.[192]

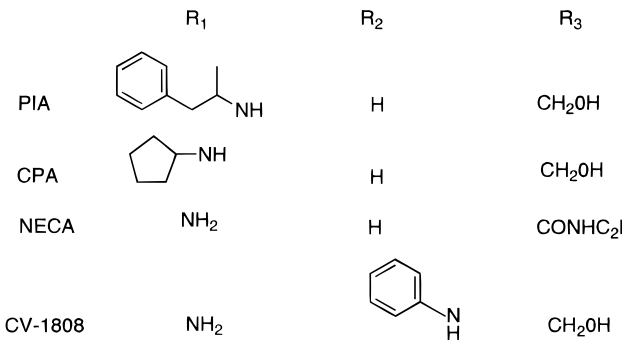
Incubating bovine ciliary muscle and trabecular meshwork strips with ET-1 resulted in their contraction indicating a possible role in outflow regulation.[193] The intracameral injection of ET-1 in concentrations ranging from 0.1 nM to 0.1 μM increased outflow facility of the living monkey eye by 22−71%. Pupil diameter was unaffected, and changes in accommodation were modest.[194] The IOP of rabbits was reduced for at least 5 days after the intravitreal injection of 2.5 μg of ET-1 or ET-3, and this was not the result of an increase in aqueous humor outflow.[191] In contrast, a considerable increase in outflow facility has been reported following the intravitreal injection of 0.5 μg of ET-1 in rabbits with IOP being lowered for 4 days.[195] The intracameral injection of picromolar doses of ET-1, ET-2, or ET-3 elicited a dose-dependent rise in the IOP of rabbits which was abolished by pretreatment with indomethacin.[196] Others have also observed an increase in IOP of 1−2-h duration in rabbits following intravitreal ET-1 which could be prevented by indomethacin pretreatment. This rise was followed by a fall in IOP of at least 3 days that was unaffected by indomethacin.[197] Sarafotoxin-S6c possesses high selectivity for the ET_B receptor,[198] and its intravitreal injection lowered the IOP of rabbits, a response unaffected by indomethacin.[199] The ocular hypotensive effect of this agonist was observed to be due to increased aqueous humor outflow in rabbits.[200] The intravitreal injections of the ET_A antagonist, BQ-123, did not alter the IOP of rabbits. However, it did blunt the increase and decrease in IOP elicited by ET-1.[201] The view has been expressed that ET_A receptors can modulate aqueous humor production whereas ET_B receptors can modulate aqueous humor outflow.[200]

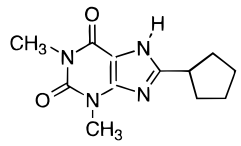
The above clearly indicates that ET could play a role in the regulation of IOP, and there is currently considerable speculation in its possible role in low-tension glaucoma (see below).

Adenosine Agonists

The acute, topical administration of the adenosine A_1 receptor agonist, (*R*)-(−)-phenylisopropyladenosine (R-PIA; 50−500 μg) lowered the IOP of rabbits. The dose of 500 μg elicited an initial increase in IOP. The effect on the contralateral eye was slight, and pupil diameter was unaffected. The ocular hypotensive response to R-PIA was blunted by the systemic administration of the adenosine A_1 antagonist, 8-cyclopentyl-1,3-dimethylxanthine (CPT). The once daily instillation of 165 μg of R-PIA for 5 days resulted in no loss of ocular hypotensive activity in rabbits.[202] In a follow-up study, the adenosine A_1 agonist, N^6-cyclopentyladenosine (CPA),







CPT

the nonselective adenosine agonist, 5^1-(*N*-ethylcarboxamido)adenosine (NECA), and the adenosine A_2 agonist, 2-(phenylamino)adenosine (CV-1808), were evaluated. The topical administration of 165 μg of CPA lowered the IOP of rabbits. A similar response to 165 μg of NECA was preceded by a rise in IOP. In contrast, 165 μg of CV-1808 only elicited an ocular hypertensive response. Hence, the reduction in IOP would appear to be mediated by adenosine A_1 receptor activation.[203] The ocular hypotensive effect of adenosine A_1 agonists in rabbits is due to a reduction in aqueous humor inflow.[204] In contrast, the rise in IOP is due to the activation of ocular adenosine A_2 receptors, resulting in an increase in aqueous humor inflow and the breakdown of the blood aqueous barrier.[205] Adenosine receptors have been demonstrated to be present prejunctionally on sympathetic nerves in the rat iris.[206] However, the IOP-lowering effect of adenosine A_1 agonists is unlikely to be due to an effect on prejunctional receptors. Firstly, ocular hypotensive responses were unaltered by sympathetic denervation. Secondly, adenosine A_1 agonists had no effect on the evoked release of [^{3}H]norepinephrine from the isolated rabbit iris−ciliary body.[205] In

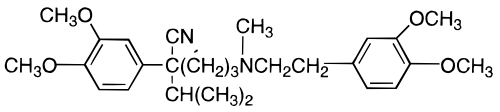
contrast, evidence for an effect on postjunctional adenosine A_1 receptors is reflected in the ability of R-PIA to suppress the accumulation of c-AMP evoked by forskolin, an effect reversed by the adenosine A_1 antagonist, CPT.[205] The ability of selective adenosine A_1 agonists to suppress stimulated c-AMP accumulation has also been shown for cultured human nonpigmented ciliary epithelial cells,[207] an effect mediated via the α-3 G-protein subunit.[208]

Low-Tension Glaucoma

A significant number of individuals can manifest glaucomatous damage to the optic nerve head but their IOPs are viewed as normal. Several observations indicate that elevated pressure alone cannot solely account for glaucoma. In Japan and the West, the incidence of optic neuropathy increases with age at the same rate yet IOP, in contrast to the West, decreases with age in Japan. In addition, IOPs are the same both for Afro-Americans and Caucasians, and for men and women, yet glaucomatous damage is appreciably higher in both Afro-Americans and women.[209] There is currently a great deal of interest in so-called low-tension glaucoma, and an understanding of its etiology would aid in the development of new antiglaucoma medications.

In contrast to open-angle glaucoma, where an elevated IOP may be associated with systemic hypertension, low-tension glaucoma is related to systemic hypotension.[210] In addition, vasospasticity can be correlated with low-tension glaucoma.[211] For example, vasospastic tendencies such as headache, migraine, and cold hands and feet are more common in women than in men as is the incidence of low-tension glaucoma,[212] leading to the concept that vascular abnormalities may be implicated in glaucomatous damage to the optic nerve head.[213] Extrapolation from cardiovascular pharmacology has led to speculation that endothelial dysfunction may contribute to low-tension glaucoma.[214] It has been found that plasma levels of ET-1 tend to be higher in individuals with low-tension glaucoma than in healthy volunteers,[215] and the intravitreal injection of ET-1 is associated with a reduction in blood flow in the rabbit optic nerve head.[216] This was also achieved both in rabbits[217] and monkeys[218] by delivering ET-1 to the optic nerve by means of osmotically driven minipumps. In addition, morphological changes to the rabbit optic nerve were similar to those present in low-tension glaucoma.[217]

The possible contributory role of vasospastic events in glaucomatous optic neuropathy has lead to the evaluation of calcium channel blockers, and these have been observed to slow the progression of low-tension glaucoma.[219] Topically applied 0.125% and 0.25% verapamil reduces the vascular resistance index in the central retinal artery of healthy volunteers[220] and increased blood velocity in the optic nerve head of volunteers, but a contralateral effect was also present.[221] The perfusion of anterior segments of the human eye with verapamil increased outflow facility, verapamil (10 nM) eliciting a peak increase of 64%.[222] The effect of calcium channel blockers on the IOP of humans remains controversial with reports of no change[223] and a small reduction in IOP.[219] Any effect, if present, is appreciably less than that of clinically used ocular hypotensive agents.



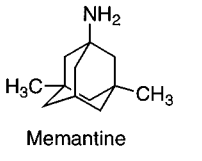
Verapamil

The importance of low-tension glaucoma is that it has focused attention on vascular parameters in the eye, and this could result in novel treatments for the disease.

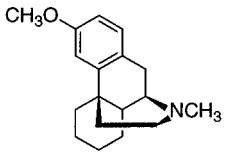
Neuroprotection

Approximately 10 000 ganglion cells are lost per year, and by age 80 an individual with normal IOP will have lost 30% of their ganglion cells. Elevated IOP can accelerate ganglion cell loss.[224] Consequently, retarding this process should reduce the loss of vision.

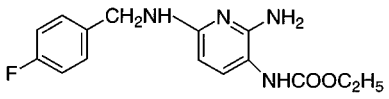
Retinal ganglion cells possess receptors for excitatory amino acids and these, when present in excess, are toxic to the cells.[225] Concentrations of glutamate in the vitreous are doubled in patients with glaucoma.[226] The long-term elevation of the vitreal content of glutamate by its repeated injection resulted in a 42% loss of retinal ganglion cells in rats. The concomitant systemic administration of the *N*-methyl-D-aspartate (NMDA) antagonist, memantine, partially blunted this effect of glutamate.[227] Intravenous infusion of the NMDA antagonist, dextromethorphan, can also reduce retinal damage in a rabbit ischemic stroke model produced by an acute elevation in IOP.[228] The intravitreal injection of flupirtine has also been observed to be neuroprotective.[229] Flupirtine is unusual in that it has negligible affinity for the NMDA receptor[229] yet it behaves in *in vitro* studies as an NMDA antagonist.[230] HU-211, in addition to being a nonpsychotropic cannabinoid, is a noncompetitive NMDA antagonist,[231] and its systemic administration can provide both short- and long-term neuroprotection in rats after optic nerve axotomy.[232] The constellation of these findings is that NMDA antagonists may have the potential to prevent neuronal loss in glaucoma.



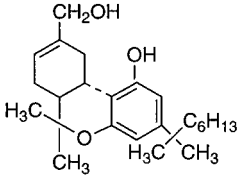
Memantine



Dextromethorphan



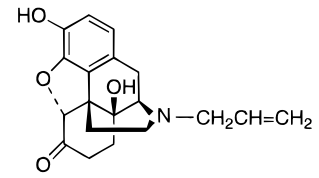
Flupirtine



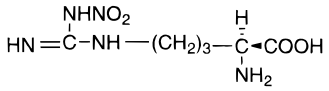
HU-211

Other miscellaneous agents which are neuroprotective to the rat retina following systemic administration are the opioid antagonist, naloxone,[233] the monoamine oxidase B inhibitor, (*R*)-(−)-deprenyl,[234] and the NOS

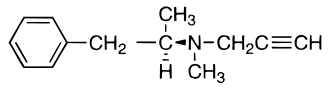
inhibitor, N^g-nitro-L-arginine.[235] In addition to the property cited, these drugs have other pharmacological actions which may or may not play a role in their neuroprotective action.



Naloxone



N^g-Nitro-L-Arginine



Deprenyl

Experiments in primates indicate that retinal ganglion cells die by apoptosis which is initiated by the deprivation of essential neurotrophic factors emitted from the brain.[236] As a corollary of this, delivery of neurotrophins to the eye may protect retinal ganglion cells from cell death.

It is to be noted that, in all the studies cited above, the drug was either administered systemically or was directly injected into the eye. Neither of these approaches is very practical in terms of long-term therapy to glaucoma patients. One potential avenue for optimizing drug delivery to the posterior part of the eye is the use of an implantable sustained-release device. This approach has been used to deliver prolonged levels of ganciclovir intravitreally for the treatment of cytomegalovirus retinitis in patients with AIDS.[237] However, the ultimate goal is obtaining an agent which possesses the appropriate physicochemical properties to attain and maintain pharmacologically effective concentrations in the posterior portion of the eye following topical administration.

Future Directions

Glaucoma is one of the leading causes of blindness, and drug therapy in the treatment of glaucoma has been focused on agents which lower elevated IOP since this is a prime risk factor in the disease process. Novel ocular hypotensive agents have recently become available clinically and offer advantages over the majority of the older medications. Ocular hypotensive agents are, and will remain for the foreseeable future, frontline drugs for combating the progressive loss of vision in glaucoma. While the cause of glaucoma is unknown and a better understanding of the pathological mechanisms in the development of primary open-angle glaucoma is required, it is known that ocular hypertension is due to an impairment in the removal of aqueous humor via the trabecular meshwork from the eye. A drug which directly enhances the flow of fluid through the trabecular meshwork is currently lacking and would represent a major breakthrough since this is the physiological process for the removal of aqueous humor from the eye. The ability of glucocorticoids to elevate IOP via an action on the trabecular meshwork is well recognized, and effort is being directed at obtaining a better understanding of this.[238] The aquaporins are water-transporting proteins which are present in a number of ocular structures,[239] including the trabecular meshwork which can express aquaporin-1 channels.[240] Their importance in aqueous humor outflow remains to be elucidated. Advances in these and other yet to be described research fronts could lead to a drug possessing a specificity of action on the trabecular meshwork to enhance outflow facility.

There is more to glaucoma than just an elevated IOP, as evidenced by the incidence of low-tension glaucoma. Whereas IOP is regulated by aqueous humor dynamics in the front of the eye, the neuropathological changes occurring in glaucoma are localized in the posterior portion of the eye. A better understanding of the processes involved in the loss of visual field is required. Agents enhancing blood flow to the optic nerve head would answer the question as to whether or not glaucoma is the result of a vascular impairment. The importance of glutamate and the neuroprotective role of its antagonists are exciting and warrant pursuit. Finally, glaucoma has a heritable component, and the tools of molecular genetics should dramatically impact on our understanding of the disease and may provide alternative therapies.[241]

By examining the trabecular meshwork inducible glucocorticoid response (TIGR) gene which is expressed in the trabecular meshwork, the gene at fault in juvenile glaucoma has been identified. Although juvenile glaucoma accounts for fewer than 1% of all cases, mutations in the TIGR gene could account for 13% of all cases of primary open-angle glaucoma.[242] The TIGR gene secretes a sticky product which has been proposed to cause increased IOP by obstructing aqueous humor outflow at the trabecular meshwork.[243]

It is clear that we are far from the end of the tunnel in terms of optimal antiglaucoma medications, and new and exciting discoveries remain to be made.

Biography

Michael F. Sugrue received his B.S. in pharmacy from the University of Glasgow, followed by a M.S. and Ph.D. in pharmacology from the same university. This was followed by three years of postdoctoral work at the University of Texas Southwestern Medical School. In 1981, he joined the MSD-Chibret Research Centre, Riom, France, as Director of Pharmacology, and in 1986 was transferred to Merck Research Laboratories, West Point, PA, as Director of Ocular Pharmacology, his current position.

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