Ann. Rev. Pharmacol. Toxicol. 1986. 26:401–26

OBSERVATIONS ON THE PHARMACOLOGY OF GLAUCOMA

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CLASSIFICATION OF GLAUCOMA

Glaucoma is a term frequently used to describe a group of diseases characterized by progressive atrophy of the optic nerve head (evidenced by cupping of the optic disc) accompanied by a gradual loss of the field of vision. The intraocular pressure (IOP) is usually elevated and if left untreated can cause further optic nerve damage and irreversible visual loss. In its early stages, cupping of the disc can be recognized as an extension of the central physiologic cup toward the superior or inferior pole of the disc. Recent histopathologic studies show that up to 35% of the axones in the optic nerve can be lost prior to the detection of a visual field abnormality (1). Since cupping can occur prior to loss of vision, the astute physician might be able to detect glaucoma in its very early stages by learning to recognize this diagnostic feature.

When glaucoma is diagnosed, a procedure called gonioscopy of the anterior chamber angle helps to differentiate between the two principal groups of glaucoma, namely open-angle and closed-angle. The most common type is open-angle glaucoma. In this condition, the aqueous humor has free access to the trabecular meshwork in the anterior chamber angle. If the trabecular meshwork in the angle is physically occluded by the bulging of the peripheral iris, the angle is considered closed and the patient is diagnosed as having closed-angle glaucoma. Many subclassifications of these two principal groups of glaucoma exist, as well as other types of glaucoma secondary to inflammation, hemorrhage, trauma, cellular or pigmentary deposits, medication, or fibrovascular membranes.

Much has been written about the etiology of glaucoma. The immediately recognizable causal factor is insufficient drainage of aqueous humor leading to elevated IOP. Most of the therapy in the past has been directed toward correction of this factor. It is now evident that elevated IOP is a secondary phenom-

0362-1642/86/0415-0401$02.00

enon and not the specific etiology. However, therapy directed to correct the basic abnormalities producing glaucoma is not yet available. Reduction of elevated IOP by various means is currently the only clinically acceptable treatment for glaucoma.

AQUEOUS HUMOR PATHWAYS

Trabecular Route

Aqueous humor enters the posterior chamber from the ciliary processes as a consequence of (*a*) hydrostatic and osmotic gradients between the ciliary process vasculature and stroma and the posterior chamber and (*b*) active ion transport across the ciliary epithelium (2–5). The aqueous humor then flows around the lens, through the pupil into the anterior chamber, and leaves the eye by passive bulk flow by way of two pathways in the anterior chamber angle. One pathway runs through the trabecular meshwork across the inner wall of Schlemm's canal and then into collector channels, aqueous veins, and the general venous circulation. This is called the trabecular or usual route.

Uveoscleral Pathway

The second pathway by which aqueous humor leaves the eye is the uveoscleral pathway. Aqueous humor flows across the iris and the anterior face of the ciliary muscle, through the connective tissue between the muscle bundles of the ciliary body, into the suprachoroidal space, and out through the sclera (5). The bulk of the outflow in experimental species would seem to be by the trabecular route (between 45 and 70%), and the uveoscleral pathway accounts for the remainder (6). However, in human eyes the uveoscleral outflow may account for about 5 to 20% of total aqueous drainage (7).

PHARMACOLOGIC AGENTS USED IN GLAUCOMA THERAPY

Drugs for the control of glaucoma can be divided into at least five subgroups: (*a*) parasympathomimetic agents, including the cholinergic and anti-cholinesterase drugs, which act primarily on the musculature of the iris and ciliary body; (*b*) sympathomimetic agents, which appear to increase the facility of outflow and may also alter aqueous humor formation; (*c*) sympathomimetic blocking agents, which appear to work mostly by reduction of aqueous humor formation; (*d*) drugs, such as carbonic anhydrase inhibitors and cardiac glycosides, that diminish the formation of aqueous humor by enzyme inhibition; and (*e*) osmotic agents, which raise the osmolarity of the plasma and thus extract fluid from the eye.

CHOLINERGIC AGENTS

It has been well known ever since the original observations of Weber regarding pilocarpine (8) and Laqueur regarding eserine (9) that the cholinergic and anticholinesterase agents lower IOP in experimental and in human eyes. Over the years many cholinergic and anticholinesterase agents have been investigated. Cholinergic agonists have been shown to decrease resistance to aqueous humor outflow (10), whereas ganglionic blocking agents and cholinergic antagonists increase resistance (10–13).

Most of the evidence suggests that iris sphincter and/or ciliary muscle contraction physically alters the meshwork configuration so as to decrease resistance; however, not all of the experimental evidence supports this strictly mechanical view of cholinergic and anticholinergic effects on meshwork function. There is the possibility of a resistance-decreasing pharmacologic effect directly on the endothelium of the trabecular meshwork or Schlemm's canal (14–15). This suggests that cholinergics have a direct cytologic effect that produces a decrease in vacuoles in the endothelial cells of the trabecular meshwork. Nomura & Smelser (16) have reported on the identification of cholinergic and adrenergic nerve endings in the trabecular meshwork. Their studies reveal a 6-to-1 proportion of cholinergic to adrenergic nerve terminals located in the posterior part of the trabecular meshwork just anterior to the insertion of the longitudinal ciliary muscle.

Topically applied acetylcholine is rapidly hydrolyzed to inactive choline; its action is too fleeting for therapeutic use as a miotic unless it is given by subconjunctival or intracameral application. When introduced into the anterior chamber during or after surgery, it brings about a marked miosis that lasts about 10 min, and it is effective even after the ciliary ganglion has been blocked by procaine. The vasodilatory action of acetylcholine is considerable, producing a marked congestion after instillation in the conjunctival sac. This is true for cholinergic drugs in general (17–20).

All of the cholinergic agents and particularly the anticholinesterase drugs cause an alteration of the blood-aqueous barrier, which leads to increased protein and cells in the aqueous humor as seen by biomicroscopy. It has been suggested that cholinergic drugs increase blood-aqueous permeability as a result of vasodilation that leads to disruption of the tight junctions in the anterior uveal blood vessels (21).

Anatomically, the longitudinal fibers of the ciliary muscle attach directly to the trabecular meshwork and to the scleral spur. It is postulated that the contractions of these muscle bundles open the trabecular meshwork and thereby enhance aqueous outflow (22). The iris itself is not directly attached to the scleral spur or to the trabecular meshwork, so that its state of contraction or relaxation does not necessarily affect outflow facility (23). Extreme miosis,

however, may alter this situation by creating a physiological iris bombé. Ordinarily, minor forward displacement of the iris is more than compensated for by ciliary muscle contraction. But if the chamber angle is very narrow, as in some cases of closed-angle glaucoma, its closure may result from the physiologic iris bombé and miosis. Parasympatholytic drugs like homatropine block contraction of the ciliary muscle and decrease outflow, as the pupil becomes coincidentally mydriatic.

Vacuoles have been demonstrated by electronmicroscopy in the endothelium of the inner wall of Schlemm's canal. In monkey eyes, pilocarpine treatment reduced the number of vacuoles by half. It was hypothesized that, by pulling and stretching of trabeculum, pilocarpine straightens and shortens the channels by which these vacuoles move through the wall of Schlemm's canal, and thus it reduces the chance of their existing in ultrathin sections (24). Studies of the trabecular meshwork and Schlemm's canal have also demonstrated pilocarpine-induced alterations in the size and shape of the intertrabecular spaces and in various characteristics including vacuolization of the inner canal wall endothelium (22, 24–26). At the present time, we do not understand what structure alterations in the meshwork account for the decrease in resistance to bulk outflow caused by ciliary muscle contraction (27). It is still not known whether the cholinergics open entirely new channels, decrease the resistance of some or all of the existing channels, widen Schlemm's canal, or produce some other critical alteration.

Cholinergic Effect on IOP

Krill & Newell (28) reported that a 2% solution of pilocarpine caused a decrease in IOP in both normal and glaucomatous eyes. The drop in IOP in normal eyes was between 8 and 38% and in glaucomatous eyes between 12 and 40%. Diurnal fluctuations in IOP were reduced. The onset of the fall in IOP was seen in 60 min and reached a maximum in 75 min after topical application in both normal and glaucomatous eyes. Very little difference in the drop in IOP was found after instillation of a single drop of either 1 or 10% pilocarpine solution (29–30). This suggests that 1% pilocarpine produces close to the maximal ocular hypotensive effect and that the higher concentration does not provide a greater response. However, the duration of response was greater with 4% than with 1% pilocarpine. There was not much difference between 8 and 4% pilocarpine in duration of response. There appears to be a reduced cholinergic effect in eyes with pigmented irides (31).

Studies have been conducted in which the iris in monkey eyes was totally removed at its root and the ciliary muscle was disinserted at the anterior end, where it normally is attached to the scleral spur (32–33). In these studies, the ciliary muscle retained its normal morphology and its contractability in re-

sponse to pilocarpine, and the meshwork exhibited its normal light and electronmicroscopic appearance (34).

In these experiments, aniridia has no effect on IOP, resting outflow resistance, or resistance to intravenous or intracameral pilocarpine (27). After total iris removal and ciliary muscle disinsertion, however, there is virtually no acute resistance response to either intravenous or intracameral pilocarpine (33). It seems, therefore, that the acute resistance-decreasing action of pilocarpine and presumably of other cholinomimetics is mediated entirely by drug-induced ciliary muscle contraction with no direct pharmacologic effect on the meshwork itself.

Cholinergic Effect on the Trabecular and Uveoscleral Routes

When perfused through the anterior chamber, radio-tagged albumin or I125 leaves the anterior chamber essentially by bulk outflow through the trabecular and uveoscleral drainage routes. In the eye that has received pilocarpine, radioactive material from the anterior chamber will also be present in the iris stroma, the iris root, the area of Schlemm's canal and the surrounding sclera, and the most anterior portion of the ciliary muscle. In the eye treated with atropine, radioactive material is found in all these tissues but, additionally, is found throughout the entire ciliary muscle and further into the choroid and sclera.

It would appear from these findings that pilocarpine and presumably other cholinergic agonists augment aqueous humor drainage through the trabecular route and diminish drainage through the uveoscleral route. This finding may be explained by the fact that when the ciliary muscle contracts in response to exogenously applied pilocarpine the spaces between the muscle bundles are essentially obliterated, resulting in a reduction in uveoscleral outflow (35). When atropine is instilled, the ciliary muscle relaxes and the spaces are widened; this will usually increase uveoscleral outflow (36).

The drainage through the trabecular route exceeds that through the uveoscleral route. Therefore, when pilocarpine is used, the net result is enhanced aqueous drainage and decreased IOP. In the monkey eye where the drainage through the trabecular and uveoscleral routes is approximately equal, pilocarpine may induce a slight rise in IOP, perhaps by inhibiting uveoscleral drainage more than by increasing trabecular drainage (37).

Cholinergic Effect on Pseudofacility

Pseudofacility is defined as the ultrafiltration component of aqueous humor formation; it is pressure sensitive and decreases with increasing IOP. The term "pseudofacility" is used because a pressure-sensitive decrease in inflow will appear as an increase in outflow when techniques such as tonography and constant pressure profusion are used to measure outflow (4, 6). Researchers

have pointed out that pilocarpine may occasionally increase pseudofacility (4, 38).

Cholinergic Effect on Aqueous Humor Formation

How cholinergic agents influence aqueous humor formation is not yet clear. Some results show an increase in aqueous humor formation, others show a decrease, and still others show no alteration at all. It appears that the effects of cholinergic drugs on aqueous humor depend on many factors, but all of the data indicate that these effects are not important in determining the drug-induced decrease in IOP.

Cholinergic Effect on Ciliary Muscle Action

The insertion of the ciliary muscle in the scleral spur provides the outflow channels with the cholinergic smooth muscle that can generate tension on the spur and thereby influence IOP. In addition, the ciliary muscle places tension on the lens zonules, which results in accommodation of the lens. These two physiological responses, even though related, are not always associated. Dissociation has been demonstrated, for example, with the use of ocuserts, by Brown et al (39), who point out that this means of administering a low but constant dose of pilocarpine produces a pronounced decrease in IOP but insignificant refractive changes. It would appear, then, that the energy exerted by the multilayered ciliary muscle in the direction of the lens is not necessarily the same degree of energy exerted in the direction of the scleral spur. Armaly (40) has shown that cholinergic action on pupil size and outflow facility cannot be dissociated.

Subsensitivity to Cholinergic Agents

Sometimes the cholinergic agent that initially was sufficient fails to control IOP in an eye with glaucoma. Loss of responsiveness in these cases may be explained by progression of the glaucoma or by the ciliary muscle becoming subsensitive to stimulation because of the chronic use of cholinergics.

In several studies it has been shown that even after long-term use of pilocarpine the ciliary muscle is still able to contract. For example, Abramson et al (41) examined presbyopic patients with glaucoma, who were on pilocarpine therapy for 1 to 14 years, and presbyopic patients without glaucoma. They were able to demonstrate that a similar increase in lens thickness in response to pilocarpine occurred in both groups.

Similar findings have been reported by Brown et al (39) who found that most glaucomatous patients had refractive changes in response to topical pilocarpine after 1 to 23 months of treatment. It would appear that the ciliary muscle still responds to pilocarpine applications over a long period of time. However, there is no question that IOP may not respond that well in all patients.

There are somewhat different results with strong anticholinesterase agents. Investigations have demonstrated the development of cholinergic subsensitivity in the iris sphincter and in the ciliary muscle with prolonged topical use of cholinesterase inhibitors like phospholine iodide (42, 43). It has been reported that repeated topical treatment with phospholine iodide in monkeys leads to subsensitive responses of accommodation and outflow facility when the animals are later challenged with pilocarpine. The recovery phase to normal sensitivity requires more than one month without drug therapy (44).

Continuous exposure to high levels of any potent cholinergic agonists induces a subsensitivity to all agonists, but subsensitivity to some agonists is more profound than others. Closer analysis of both in vivo physiological and in vitro receptor binding data suggests that differential partial agonism alone may not explain differing agonist potencies in the subsensitive eye. This might be explained by the presence of two or more distinct populations of relevant muscarinic receptors in the iris sphincter and ciliary muscles of cynomolgus monkeys (45).

Anticholinesterase Agents

Isofluorophate-induced miosis is of rapid onset and prolonged duration. In the normal human eye, miosis begins within 5 to 10 min and is maximal within 15 to 20 min. The duration of miosis is from one to four weeks. The maximal miosis appears to be brought about by a solution of 0.05%. A suitable concentration of diisopropyl fluorophosphate (DFP) or isofluorophate eyedrops for therapeutic purposes is 0.01%. The watery drops are unstable, but oily drops of 0.025 to 0.1% in anhydrous peanut oil retain their activity for almost two months.

Topically applied DFP or isofluorophate reduces the IOP of the normal eye with maximal hypotensive effect within 24 hr. The return to normal IOP requires about one week. Ciliary spasm caused by isofluorophate treatment results in myopia that is maximal and lasts for three to seven days (46–47).

Topically applied anticholinesterase agents may be absorbed systemically and may produce depression of serum and red cell cholinesterase. The fewest systemic effects are seen with echothiophate (48).

ADRENERGIC AGENTS

Adrenergic Receptors in the Eye

After adrenergic receptors were classified into α- and β-receptors and then further classified into α_1, α_2, β_1, and β_2, most of these receptor types were found to be present in eye tissues. Even though the full distribution of these receptor subpopulations in eye tissues has not yet been clearly delineated, data exist to indicate that the receptors on the iris dilator muscle are mainly of the α_1

type, and the receptors populating the ciliary body stroma and epithelium and the ciliary blood vessels are mainly of the β_2 type. Both β_2- and α_1-receptors are believed to be present in the trabecular meshwork. The receptors in the retina are believed to be mainly of the α_2 type.

Many agents have been developed that affect one or more subpopulations of receptors. This work has led to the discovery of a number of adrenergic drugs that lower IOP. Most of these agents are able to markedly reduce IOP without the side effects typically associated with parasympathomimetic drugs, but they do have other undesirable features.

Mechanism of Action of Adrenergic Agents

The mechanism of action by which adrenergic agents lower IOP has not been completely elucidated. The present state of knowledge suggests that their action is related to their effects on the various α- and β-receptors located either in the outflow channels or in the inflow apparatus of the ciliary body epithelium and blood vessels. There is also evidence indicating that stimulation of the α-receptors in the outflow channels results in an increase in the facility of aqueous outflow (49–52).

It has been suggested that sympathomimetic drugs reduce the rate of aqueous secretion by stimulating β-receptors (50, 53). A reduction in aqueous secretion could result from a reduced blood flow to the ciliary processes, which has been shown to occur with sympathetic stimulation, but it could also result from direct action on the ciliary epithelium (54). An excellent attempt has been made to review the body of data and analyze the many differences in findings, particularly the small effects seen after pharmacologic doses in several species (55, 56).

Epinephrine

Epinephrine (adrenaline) has been used for many years to reduce IOP in patients with simple glaucoma. Its action in reducing IOP appears to result from a combination of many factors, none of which are absolutely established.

Glaucoma patients differ in their responses to epinephrine treatment. Some patients respond within hours, others respond only after continued use for weeks or months, and some do not respond at all to topically administered epinephrine. Differences in response may reflect the extent of the disease, the damage to the anterior chamber angle, the amount of pigment in the eye, or other factors presently unknown. In some patients, epinephrine initially reduces IOP but later becomes ineffective. This type of reduced response might be due to loss of adrenergic receptors with continued epinephrine treatment, as has been recently demonstrated in the cornea (57). Age may also play an important role in the response of the human eye to epinephrine (58).

Neufeld (59) has pointed out that topically administered epinephrine may

have an influence on the ciliary processes and the formation of aqueous humor. It influences aqueous secretion associated with active transport of ions by stimulating a cyclic adenosine monophosphate (AMP) mediated pathway in the nonpigmented epithelium. In addition, it probably influences ultrafiltration that is due to pressure-dependent flow by ordering the profusion pressure in the vascular bed. However in what direction, that of increased or decreased inflow, is the net effect of epinephrine? The observations of Macri (60) suggest that epinephrine decreases ultrafiltration. Recent aqueous fluorophotometric measurements, however, suggest that topical epinephrine increases inflow (61).

Early tonographic studies led to the conclusion that topical epinephrine acts primarily by decreasing the rate of aqueous humor production (62–65). Many subsequent clinical studies have demonstrated improvement in outflow facility with topical epinephrine treatment. Ballintine & Garner (66) found that outflow facility improved by 50% in almost half their patients within one month after the addition of epinephrine to the treatment regimen. Becker et al (67) also reported significant increases in outflow facility three to six months after initiation of epinephrine treatment. In a more recent study (68), it was confirmed that after several weeks of epinephrine therapy outflow facility was improved by 30%.

Yablonski (69) has pointed out that since epinephrine is an α-, β_1, and β_2-agonist, it is not surprising that its effect on IOP is the result of several independent alterations in the aqueous humor dynamics of the eye. The study concluded that IOP is determined by the interaction of four independent factors: (*a*) the rate of aqueous humor formation, (*b*) the outflow facility, (*c*) uveoscleral flow, and (*d*) episcleral venous pressure. All but the last—episcleral venous pressure—are affected by topical epinephrine.

CLINICAL USE OF EPINEPHRINE Topical administration of epinephrine reduces IOP in patients with open-angle glaucoma but has only a slight effect in normal eyes (70). Although concentrations as low as 0.125% do have some ocular hypotensive effect, a 1% concentration is substantially more effective (71). Epinephrine constricts conjunctival vessels, contracts the pupil dilator muscle, and may dilate the pupil after topical application. It relaxes the ciliary muscle only slightly, so cycloplegia does not occur.

Topical application of epinephrine often results in ocular discomfort and conjunctival irritation with transient burning or stinging, lacrimation, and pain around or in the eye. Occasionally, conjunctival allergy will occur. Adverse corneal effects include epithelial edema, endothelial cell toxicity, and adrenochrome deposits (72). Visual haze and, rarely, central scotoma can occur but are reversible when epinephrine therapy is discontinued. Dramatic visual acuity decreases have been reported occasionally, especially in aphakic patients (72).

In 20 to 30% of aphakic patients, macular edema occurs but, again, usually disappears when epinephrine treatment is discontinued (73).

The following systemic effects have been associated with topical application of epinephrine: palpitations, faintness, tachycardia, extrasystoles, cardiac arrhythmia, hypertension, anxiety, trembling, sweating, and pallor. Many of these systemic side effects can be avoided by punctal occlusion for 15 to 30 sec after application of the drug. Punctal occlusion prevents drainage of the drug into the nasopharynx, where it may be systemically absorbed (72).

Dipivefrin (Propine®)

Dipivalyl epinephrine (dipivefrin) is a prodrug formed by diesterification of epinephrine. It has been shown to lower IOP when given in concentrations approximately one-tenth of those used for epinephrine (74). Most glaucoma patients respond well to dipivefrin treatment (75, 76). Dipivefrin was developed because of concern about the side effects of epinephrine.

Epinephrine has been established as a valuable drug for glaucoma therapy. However, its use is often limited by a high incidence of adverse reactions. Some of these reactions, such as reactive hyperemia, blepharitis, and localized pain and itching, may be related to the local concentration of epinephrine or its degradation products in the conjunctival sac. The fact that the maximum effect of dipivefrin on IOP occurs with a concentration one-tenth (0.1%) of that required for epinephrine (1%) and the fact that dipivefrin must be activated by an esterase indicate that it can be used to avoid the side effects of epinephrine on the conjunctiva and lids. Dipivefrin resides in the conjunctival sac in a molecular form other than epinephrine, thus decreasing the likelihood of a conjunctival or allergic reaction to epinephrine. In a 0.1% concentration, dipivefrin has demonstrated ocular hypotensive effectiveness and good tolerance in patients who have displayed intolerance to epinephrine (77).

It would also seem that systemic reactions to epinephrine, such as cardiac arrythmias and elevated systemic blood pressure, are less likely to occur with dipivefrin, since these reactions relate to the total amount of epinephrine administered. As similar intraocular concentrations of epinephrine are thought to result with topical administration of both dipivefrin and epinephrine, one would not anticipate any significant difference between dipivefrin and epinephrine in the incidence of aphakic epinephrine-induced maculopathy.

α-Adrenergic Agents

α-ADRENERGIC AGONISTS Drugs with agonistic effects on either the α_1- or α_2-receptors are currently not being used for the treatment of glaucoma, mainly because the efficacy of available α-agonists has not been proven. Topically applied phenylephrine produces a small reduction in IOP, but it is much less

effective than topical epinephrine. Phenylephrine pivalate penetrates the eye much better than phenylephrine, but its effect on IOP is still minimal. Naphazoline, tetrahydrozaline, and oxymetazoline are used clinically as vasoconstrictors and also have limited effects on IOP. Topically applied to rabbit eyes, methoxamine produced a dose-related early rise in IOP followed by a reduction that lasted six to eight hours.

Selective α-adrenergic agents may have value in the management of glaucoma, but we are just beginning to understand their actions in the eye. Increased understanding should aid in the selection of drugs to treat elevated IOP.

Clonidine Clonidine is a relatively specific α_2-adrenergic agonist used clinically as a potent systemic antihypertensive drug (78). Topically applied in normal and glaucomatous human eyes, clonidine causes a significant decrease in IOP (79–84). In one study clonidine had no effect on the tonographic facility of outflow (82), but in another study clonidine caused a 5 to 15% improvement in outflow facility (84).

Topically applied clonidine has both local and systemic circulatory effects. It decreased episcleral venous pressure in both treated and untreated fellow eyes of normal and glaucomatous human subjects (81–83). In concentrations of 0.25 and 0.5%, clonidine caused a dose-dependent decrease in the diastolic and systolic ophthalmic arterial pressures in patients with open-angle glaucoma (85–86), but in a 0.125% concentration it caused little or no decrease in systemic blood pressure (79, 80, 83–85). Clonidine has been shown not to affect pupil size (79–80) or visual acuity (80).

In one study by Allen & Langham (87), topically applied 0.125% clonidine caused a significant decrease in the IOP of treated eyes and a small but significant decrease in untreated fellow eyes. Aqueous humor flow was significantly lower (by 21%) in clonidine-treated eyes than in untreated fellow eyes. The decreases in IOP and aqueous humor flow were associated with decreases in pupil size in both eyes (although greater in the clonidine-treated eyes) and in systolic blood pressure. It appears from these findings that topically administered clonidine has both local and systemic effects.

The mechanism for the decrease in aqueous humor flow is unclear. Clonidine may decrease flow by reducing ciliary blood circulation. Local and systemic effects could be involved in the reduction of ciliary blood flow. Clonidine may also decrease aqueous flow through its effect on α-adrenergic receptors in the ciliary body, but other studies of α-adrenergic agents have demonstrated very small and usually insignificant effects on flow (61, 88–91).

The possibility remains that the effect of clonidine on aqueous humor flow may be independent of and unrelated to its α-adrenergic actions. Future study of other relatively specific α-adrenergic drugs should help to better define the effects of these drugs on aqueous humor flow in the human eye.

α-ADRENERGIC ANTAGONISTS A number of α-adrenergic blocking agents given systemically or topically have been shown to lower IOP in experimentally ocular hypertensive rabbits (92–94).

Dibenamine has to be administered intravenously and lowers IOP by reducing the secretion of aqueous humor (95). Phenoxybenzamine, or dibenyline, has an action similar to that of dibenamine, i.e. the blockade of α-receptors. It reduces IOP in acute angle-closure glaucoma but appears to have no effect on IOP in simple glaucoma (96).

Phenoxybenzamine, a noncompetitive long-acting antagonist, has been shown to lower IOP in normotensive and in experimentally ocular hypertensive rabbits when given systemically or topically (92, 97). Yohimbine, an indolealkylamine alkaloid with chemical similarity to reserpine, is a selective α_2-blocker. In rabbits, yohimbine lowers IOP (98), but its ocular hypotensive effect in higher mammals has not been demonstrated.

Prazosin In 1979, Smith et al (94) reported that topical application of concentrations of 0.0001 to 0.1% of the α-adrenergic antagonist prazosin reduced IOP in normotensive rabbits. The maximum effect of 0.1% prazosin occurred at two hours and lasted for almost eight hours; the drop was about 6 to 7 mm Hg. Sympathectomy did not eliminate the ocular hypotensive action of prazosin, however, and reduced it only slightly. It appears that prazosin may not lower IOP by blocking endogenous catecholamine activity. In the studies of Smith et al, the drop in IOP was not associated with a fall in systemic blood pressure.

Krupin et al (99) confirmed the observation that the effect of prazosin on IOP in rabbits was not due to a systemic effect on blood pressure. They also demonstrated a decrease in the rate of aqueous humor formation and showed that prazosin-induced reductions in IOP could be prevented by systemic pretreatment with the α-adrenergic blocker phentolamine, but not with propranolol or atropine.

β-*Adrenergic Agents*

β-ADRENERGIC AGONISTS At the molecular level, stimulation of β-adrenergic receptors leads to activation of membrane-bound adenyl cyclase and an accelerated rate of production of intracellular cyclic AMP. The ciliary processes contain predominantly β_2-receptors (100); β_2 stimulation is an especially effective way to lower IOP (101). However, as has been pointed out by many researchers (55, 102–106), the use of β_2-agonists is often accompanied by disappointing results, including rapid loss of ocular hypotensive effect, ocular hyperemia, and tachycardia.

Reviews by Mishima (55) and Potter (56) suggest that α-adrenoreceptors mediate increases in true outflow while β-adrenoreceptors mediate changes in inflow. The site of action for the effects of α-reception on outflow is probably

trabecular, and the effects are modest in comparison with increases produced by the action of cholinergics on the ciliary muscle. The site of action for the β-agonist-induced reduction in inflow is in some part of the ciliary epithelium, possibly the nonpigmented epithelium. Uveoscleral flow is also increased by adrenergic agonists (6, 107–109).

Isoproterenol, a β-adrenergic agonist, has been found to lower IOP (102); however, its clinical usefulness is limited by erratic results and consistent production of tachycardia in elderly patients (102, 103). The results of several studies (50, 103, 110) suggest that isoproterenol reduces aqueous humor formation, but the studies of Bill (108) suggest that the drug increases aqueous humor formation. Two other β-adrenergic agonists, salbutamol and metaproterenol, have been found to increase aqueous formation (111–113).

Brubaker & Gaasterland (113) were unable to demonstrate either a lowering of IOP with isoproterenol or an effect of isoproterenol on the flow of aqueous humor in the normal eye. It may be that the effect on flow in their studies was too small or too transient to be detected with their study methods or at the time period they chose to measure IOP. The effect of isoproterenol on IOP might, of course, be due to other factors that were not measured, such as uveoscleral flow.

Selective β_2-agonists Several β-agonists (salbutamol, terbutaline, soterenol) that have greater affinity for β_2-receptors than for β_1-receptors are being used systemically to treat asthma. These drugs have also been shown to lower IOP in monkeys (104) and humans (114–115). Topical application of 4% salbutamol significantly lowers IOP in human eyes. The reduction in IOP seems to be mainly a result of reduction in aqueous humor production; however, an increase in both trabecular and uveoscleral outflow may also play an important role (116). Substantial conjunctival injection and eye pain experienced by patients using the drug, as well as rapid tachyphylaxis developing within a few weeks, limit the usefulness of this drug for the treatment of glaucoma.

Nonselective β-agonists Isoxuprine and nylidrine are nonselective β-agonists. They are phenylisopropylamines, very similar to ephedrine, and they act indirectly by increasing the β-vascular effect of endogenous catecholamines. Topical isoxuprine and nylidrine in 1% solution have been shown effective in lowering IOP in glaucomatous eyes but have also been associated with miosis and conjunctival hyperemia (117).

β-ADRENERGIC ANTAGONISTS A variety of β-adrenergic antagonists have been reported to lower IOP when administered topically or systemically to normal volunteers or glaucomatous patients (118). Topical β-blockers have become the most popular agents for the medical management of glaucoma.

Many clinical trials and several years of clinical experience with thousands of patients receiving these drugs strongly support excellent long-term ocular hypotensive efficacy.

Mechanism of action of β-adrenergic antagonists Most of the data for experimental animals, particularly for those with artificially elevated IOP, suggest that the reduction of aqueous humor inflow is a local action of the drug upon the eye. The decrease in IOP sometimes seen in the untreated contralateral eye after topical administration of a β-adrenergic antagonist in the treated eye is usually less than the decrease in the treated eye. It has been suggested that the effect in the treated eye is a local phenomenon and that the effect in the contralateral eye is a result of systemic absorption.

Although the existing data support a local action of the β-adrenergic antagonist timolol, there still remains a question as to whether the ocular hypotensive activity is related directly to an ability to block β-adrenergic receptors. Schmitt et al (119) could find little relationship between the ability of timolol, propranolol, alprenolol, oxprenolol, and practolol to antagonize the IOP lowering effect of isoproterenol in water-loaded rabbits and the ability of these agents to lower IOP. The ability of these β-adrenergic blocking agents to antagonize isoproterenol-induced elevation of aqueous humor cyclic AMP was also not correlated with their ocular hypotensive activity.

Alprenolol effectively lowered IOP but exhibited little or no activity in antagonizing either the effects of isoproterenol on IOP or cyclic AMP. Oxprenolol, on the other hand, had little or no ocular hypotensive activity but was very active in antagonizing both actions of isoproterenol. All of these agents penetrated the anterior chamber readily. At this point, there is no explanation for the fact that both β-adrenergic antagonists and agonists lower IOP and reduce aqueous flow in humans and animals. There may be an as yet undefined mechanism unrelated to classical β-adrenergic blockade that accounts for the hypotensive action of these agents.

The formation of aqueous humor appears to decrease after topical treatment with timolol (120–121), while the outflow facility seems to remain unchanged (68, 122). The ability to decrease the formation of aqueous humor implies that timolol is active in the ciliary processes and affects secretion or ultrafiltration or both.

The exact mechanism by which topical β-blocking agents affect the formation of aqueous humor is not known. Perhaps timolol and other β-blocking agents are interfering with the normal β-adrenergic stimulation of the ciliary processes that promotes the everyday production of aqueous humor. There is some evidence that agents such as epinephrine or isoproterenol may transiently increase the formation of aqueous humor in rabbits, monkeys, and humans (61, 108, 123). Whether the primary influence of the topical β-blockers is exerted

on the vascular smooth muscle or on the epithelium of the ciliary processes is not known (124).

It is also possible that the β-adrenergic antagonism of the vascular smooth muscle receptors may block vasodilation, promote vasoconstriction in the anterior ciliary arterioles, and thus reduce ultrafiltration by decreasing the capillary perfusion pressure. This reduction in blood flow would also indirectly decrease secretion. As Bartels & Neufeld (124) have pointed out, the β-blocking agent may directly block tonic stimulation to secretory epithelium. Such a mechanism mediated by cyclic AMP has been found in many transporting epithelia and has been suggested but not demonstrated in the ciliary processes.

In summary, the mechanism of action of the β-blocking agents in lowering IOP has not been fully established. It has been shown that β-blockers substantially reduce aqueous humor formation, and it has been suggested that they may do this independent of their interaction with β-adrenergic receptors of the ciliary processes. Recently, Liu & Chiou (125) have shown that the *dextro*-isomer of timolol, which has low affinity for β-receptors, may be as effective in decreasing aqueous flow as the *levo*-isomer of timolol. This may support the idea of some other mechanism being responsible for the decrease in IOP.

Agents that Affect Both α- and β-Receptors: Labetalol

Labetalol is a unique compound with both α- and β-blocking activity. The drug has been used for the treatment of patients with systemic hypertension resulting from a variety of etiologies (126). In rabbit eyes, topically applied labetalol in concentrations ranging from 0.01 to 1% was shown to reduce IOP (127). The mechanism by which this pressure reduction occurs is unclear. It seems that some mechanism other than α- and β-blockade is involved (128). The ocular hypotensive effect of labetalol in humans is negligible (129–130).

Agents that Affect Postganglionic Neuron Function

GUANETHIDINE The effect of guanethidine on the sympathetic nervous system might continue through several phases, depending on the frequency and the duration of therapy. Initially, guanethidine interferes with norepinephrine released from postganglionic sympathetic nerves on stimulation. It also interferes with the re-uptake of norepinephrine from the synapse into the sympathetic nerve terminals (131). Long-term guanethidine therapy leads to depletion of norepinephrine in nerve terminals (chemical sympathectomy). This reaction is reversible within a week or two after discontinuation of guanethidine therapy (132).

Topically administered guanethidine in concentrations ranging from 1 to 10% significantly reduces IOP in humans; some tachyphylaxis has been reported with long-term therapy. The mechanism of action is presumed to be

through amplification of intrinsic adrenergic mediators. Early mydriasis, conjunctival injection, and corneal epithelial toxicity evidenced by punctate keratitis have been reported with topical guanethidine treatment. With chronic therapy, when partial adrenergic denervation develops, miosis and ptosis may occur.

Medications combining guanethidine and epinephrine in a variety of concentrations have been found to be clinically useful; guanethidine seems to potentiate the ocular hypotensive effect of epinephrine (133–134).

Two other drugs that may affect postganglionic function are 6-hydroxydopamine and pargyline. 6-Hydroxydopamine completely and selectively destroys peripheral sympathetic nerve terminals in the anterior segment of the eye. This reversible chemical sympathectomy causes a supersensitivity to exogenously administered catecholamines (135). 6-Hydroxydopamine induces supersensitivity to topically applied epinephrine in patients with open-angle glaucoma (136). Pargyline is a monoamine oxidase (MAO) inhibitor; its application to the eye may activate intrinsically present as well as extrinsically administered epinephrine to cause a reduction in IOP (137–138).

Agents that Stimulate Adenylate Cyclase Directly: Forskolin

Forskolin is a dipertene that acts directly on the enzyme adenylate cyclase without cell surface mediation to increase intracellular levels of cyclic adenosine monophosphate. Forskolin has been shown to lower IOP in experimental animals and in humans (139–142).

Cannabinoids

Cannabinoid drugs—Δ9-tetrahydrocannabinol (THC), SP-1, and SP-106—have been shown to decrease IOP in intact, normal eyes and in ganglionectomized eyes (143), which indicates that these drugs may have ocular and extraocular sites of action. The direct effect of THC on IOP in the ganglionectomized eye could be inhibited in part by phenoxybenzamine and sotalol, which suggests that THC has local α- and β-adrenoceptor activity. Cannabinoids also seem to have an effect on the central nervous system, evidenced by the observation that in rabbits ganglionectomy and preganglionectomy partially inhibit the fall in IOP produced by these drugs.

Drugs that Affect Sodium/Potassium ATPase

SODIUM VANADATE Vanadate given either as sodium metavanadate (NAVO-3) or sodium orthovanadate (NAVO-4) lowers IOP in rabbits (144). The fall in IOP is not associated with significant changes in outflow facility or episcleral venous pressure. It is possible that this drug may reduce the rate of aqueous humor formation as a result of inhibition of ciliary epithelium sodium/

potassium ATPase. In rabbits, chronographic studies have shown an aqueous humor flow decrease of approximately 30% two hours after topical administration of 1% vanadate (144, 145).

Using fluorometric techniques and agents to enhance penetration (DMSO and Tween-80), Podos et al (146) studied the effects of topically applied 1% sodium vanadate (NAVO-3) on IOP, outflow facility, and aqueous humor flow in cynomolgus monkeys. In this study, vanadate significantly reduced IOP. No alteration in outflow facility was demonstrated, and the reduction in IOP was associated with a 30% reduction in aqueous humor flow as measured by fluorophotometry.

Vanadate has been shown to stimulate adenylate cyclase activity in isolated membrane preparations (147). There is also evidence that vanadate stimulates monkey ciliary body, iris, and adenylate cyclase in vitro. Cyclic AMP and its analogs are reported to increase outflow facility (64). Another report (140) indicates that forskolin lowers IOP in rabbits, monkeys, and humans when topically applied. The effect was shown to be a result of a reduction in aqueous flow.

CARDIAC GLYCOSIDES Cardiac glycosides, such as systemically administered ouabain, have also been shown to lower IOP. These drugs are presumed to act by interfering with the sodium/potassium pump, located in the nonpigmented ciliary epithelium, and by reducing aqueous formation.

Prostaglandins and Corticosteroids

In addition to the well-known ability of prostaglandins to raise IOP in rabbit eyes, it has been reported recently that moderately low doses of PGE-2 and PGF-2a significantly reduce IOP in a variety of experimental animals. These studies suggest that prostaglandins may serve as an endogenous regulator of outflow facility in the trabecular meshwork if these autocoids were produced and secreted by human trabecular cells (148). Physiological levels of glucocorticoids may regulate prostaglandin production within the trabecular meshwork. Therefore, studies of endogenous prostaglandin production by trabecular cells could provide new clues to the pathogenesis of a number of glaucoma syndromes including primary open-angle glaucoma and steroid-induced glaucoma (148).

It has also been suggested that epinephrine stimulates the formation and release of prostaglandins, and perhaps that is one of the mechanisms by which epinephrine lowers IOP (149). This would suggest that agents inhibiting the release of prostaglandins, such as nonsteroidal anti-inflammatory drugs like aspirin and indomethacin, could reduce the effectiveness of topically applied epinephrine or perhaps even of β-blocking agents such as timolol.

Dopamine in the Eye

Until recently, investigations into the role of dopamine (DA) in the eye have focused mainly on its function as a neurotransmitter in the retina. In contrast to extensive studies on retinal DA, only a few studies dealing with DA in the anterior segment of the eye have been published.

In an early study of DA in nonretinal ocular tissues, it was reported that DA given either topically or intravitreally lowered IOP in rabbits with α-chymotrypsin-induced ocular hypertension (150). Furthermore, at doses of 10 μg and 100 μg, DA decreased IOP without concurrent mydriasis, which suggests a dissociation of ocular hypotension from α-adrenergically mediated mydriatic response. DA-induced ocular hypotension was abolished by intramuscular haloperidol but not by intravenous propranolol. Cervical ganglionectomy had no effect on the hypotensive response to DA. Thus, it was concluded that (*a*) DA is capable of lowering rabbit IOP by activating specific DA receptors, and (*b*) this action is independent of the ocular sympathetic system. In another study in which a higher topical dose of DA was administered, a rise in IOP was reported (105). Thus, DA may elicit different IOP responses, depending on the dose.

Investigation into the mechanisms underlying the ocular action of DA indicates that this agent can influence aqueous humor formation. Topical administration of DA has been reported to increase aqueous humor formation in rabbits (151). These DA-induced increases in aqueous formation and in permeability were blocked by the nonselective α-adrenoceptor antagonist phentolamine, but DA antagonists such as butaclamol and chlorpromazine were relatively ineffective. This finding implicates the activation of the adrenergic receptors rather than specific DA receptors as a mechanism of action.

Other investigators have reported that DA reduces aqueous humor formation. In the enucleated perfused cat eye, arterial infusion of DA produced immediate vasoconstriction and a 55% reduction in the rate of aqueous humor formation (152). Since phenoxybenzamine blocked both of these effects, it is likely that the activation of α-adrenergic receptors was involved in this action. When these findings are taken together, they indicate that DA can alter the rate of aqueous humor formation through its actions on the vasculature and/or secretory processes. However, there is no evidence for the involvement of specific DA receptors in these actions at this time.

One of the problems in using DA as an agonist to study the DA system is its relative lack of specificity. It is well known that DA is capable of activating α- and β-receptors as well as DA receptors (153). Furthermore, DA receptors themselves are classified into at least two subtypes (154). The activation of Type 1 DA receptors (DA-1) is linked to renal vasodilation and stimulation of adenylate cyclase. The activation of Type 2 DA receptors (DA-2) is associated

with such responses as inhibition of both prolactin release and neurotransmission. Unlike DA-1 responses, DA-2 responses are not mediated by stimulation of adenylate cyclase. Clearly, there is a need to use more selective DA agonists and antagonists in order to investigate further the role of a DA system in regulating IOP. Although no systematic evaluation of the selective DA agonists and antagonists has been published, there are several reports indicating that these agents may possess ocular hypotensive activity.

A rigid analog of DA, 6,7-dihydroxy-2-aminotetralin (6,7-ADTN) is a DA-1 agonist. The topical administration of 6,7-ADTN has been shown to lower IOP in albino New Zealand rabbits and to suppress ocular hypertension after water loading (155). Since superior cervical ganglionectomy attenuated the ocular hypotension induced by 6,7-ADTN, the mechanism of this hypotensive action appears to involve the modulation of ocular sympathetic nervous activity.

LY 141865 is a potent and selective DA-2 agonist that produced a bilateral decrease in IOP when administered topically to albino New Zealand rabbits (155). It also suppressed IOP recovery rate after intravenous infusion of hypertonic saline in rabbits. As with 6,7-ADTN, the ocular hypotension produced by LY 141865 was attenuated by surgical sympathectomy.

Pretreatment with domperidone, a DA-2 antagonist, has been reported to inhibit the ocular hypotensive effects of bromocriptine and pergolide, two ergot derivatives (156). Furthermore, the ergot derivatives were shown to depress the rate of IOP recovery but had a minimal effect on outflow facility. It was concluded that the most probable site of action is the inflow site via the activation of DA-2 receptors.

Topical administration of both pergolide and lergotrile also significantly decreased IOP in the Cebus monkey (157). Interestingly, oral administration of bromocriptine has been reported to reduce IOP in normal human volunteers without changing heart rate or blood pressure (158). Moreover, a recent report (159) indicates that topical administration of bromocriptine is also effective in unilaterally lowering IOP in normal human volunteers.

In terms of DA antagonists, only the ocular effects of the butyrophenones and phenothiazines have been reported. Using the cat constant pressure perfusion model, Chiou (160) reported that the topical administration of haloperidol produced an initial increase in aqueous humor outflow followed by a decrease in inflow. Haloperidol and several other butyrophenones were also reported to suppress IOP recovery rate after intravenous infusion of hypertonic saline in rabbits. Chiou concluded that in rabbits this class of DA antagonists may have ocular hypotensive activity by inhibiting aqueous humor formation.

Chlorpromazine, a DA antagonist belonging to the phenothiazine class, has been reported to decrease IOP in rabbits and cats when administered intramuscularly (161, 162). When topically administered, however, it was irritating and failed to lower IOP. Since a study to identify the specificity of action has

not been performed, it is not known if the ocular effects of the butyrophenones and phenothiazines are related to a blockade of the DA system.

In summary, the role of DA in the anterior portion of the eye is not clear. Nevertheless, there are several reports indicating that agents known to influence the DA system can lower IOP in vivo. Further investigations in this area of research should (*a*) identify which subclass of DA receptors, if any, is involved in regulating IOP, and (*b*) determine the mechanism of action.

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