0031-6997/91/3303-0133$02.00/0
PHARMACOLOGICAL REVIEWS
Vol. 33, No. 3

Adrenergic Pharmacology of Aqueous Humor Dynamics

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I. Introduction

ONE of the presumed functions of the sympathoadrenal system is to aid in the maintenance of homeostasis throughout the body. Friedenwald and Buschke (46) were two of the first scientists to speculate that a humoral adrenergic component of the autonomic nervous system had a modulatory role in aqueous humor dynamics. Moreover, they suggested that some forms of glaucoma were probably due to derangements in local control of ocular fluid homeostasis. Similarly, Langham (96) has attributed glaucoma to vascular dysfunction that develops from a failure of adrenergic mechanisms to regulate aqueous dynamics. In this regard, Linnér and Prijot (106) demonstrated the modulatory influence of noradrenergic neurons on steady-state intraocular pressure (IOP) by the technique of surgical denervation of the sympathetic input to the eye. It is interesting that a similar technique had been tried much earlier in treating patients with glaucoma (74).

Since these early observations, adrenergic drugs have become mainstays in the topical therapy of chronic, simple (open-angle) glaucoma. The nonselective adrenergic agonist epinephrine has been used therapeutically for more than 40 years although its mechanism(s) of action continues to be the subject of considerable conjecture. More recently, the availability of relatively selective adrenoceptor agonists and antagonists, the discovery of drug alteration of adrenergic neuron function, and the clinical utility of the β-adrenoceptor antagonist timolol in glaucoma have engendered new interest in adrenergic modulation of aqueous humor dynamics.

Early attempts at pharmacological manipulation of IOP focused on stimulation of postjunctional α- and/or β-adrenoceptors by agonists. Later, antagonists of α- and β-adrenoceptors were studied and found to be effective ocular hypotensive agents. Eventually it was demonstrated that drugs capable of suppressing noradrenergic neuron function were capable of altering aqueous humor dynamics.

The objective of this review is to acquaint the reader with the effects of adrenergic drugs on aqueous humor dynamics and the implications of these findings in glaucoma therapy in the face of the controversial nature of much of the experimental and clinical evidence.

II. Determinants of Intraocular Pressure

Aqueous humor is produced by the processes of the ciliary body and drained through outflow channels to

extraocular veins. Circulation of aqueous humor is a vital element in the maintenance of normal intraocular pressure and in the supply of nutrients to avascular portions of the eye, namely the lens and the cornea. Intraocular pressure is determined by the delicate balance between aqueous humor formation, aqueous humor outflow, and episcleral venous pressure; aqueous formation and ocular blood flow are in turn influenced by IOP. Abnormalities in IOP may be viewed, in part, as a vascular problem in that production and outflow of aqueous humor are dependent on fluid movement through vessels under adrenergic and/or autoregulatory control. Circulatory disturbances of aqueous humor, principally decreased outflow but in some cases hyperproduction of aqueous with normal outflow, lead to an abnormally elevated IOP that may ultimately lead to damage of the optic nerve and blindness.

One can measure IOP directly by manometric methods or indirectly by tonometric methods (32). The direct cannulation method involves the insertion of a hypodermic needle into the anterior chamber of the eye and may initially result in damage and some loss of fluid from the eye. The indirect methods involve measurement of pressure by indentation or applanation of the cornea (143). These indirect methods measure force on an area of the cornea as an index of pressure in the eye. The instruments used, particularly the applanation tonometer, require careful calibration and it is to be remembered that there are dissimilarities in plasticity of the cornea between different species.

A. Formation of Aqueous Humor

Aqueous humor is formed in the posterior chamber by the ciliary processes by three physiological mechanisms: diffusion, ultrafiltration, and active secretion (see fig. 1). The latter process is an active, energy-requiring process whereas the former processes are passive. Ultrafiltration is the hydrostatic (pressure-dependent) component of formation resulting from arterial blood pressure and pressure in the vessels serving the ciliary body. The bulk of formation of aqueous humor is a product of active cellular secretion by the inner, nonpigmented ciliary epithelium that contains the enzymes ATPase and carbonic anhydrase (28, 33). The rate of aqueous humor formation differs between species, being about 2 μl/min in humans and 3 to 4 μl/min in rabbits (178). Once formed by the ciliary processes in the posterior chamber, the aqueous humor flows through the pupil (between the posterior iris and the lens), around the anterior chamber, and into the outflow system at the peripheral angle of the anterior chamber.

Methods of measuring the rate of aqueous formation consist of: 1) measuring a radioactive (108) or dye (73) substance's rate of appearance in or disappearance from the aqueous humor, or 2) calculating the flow from a formula that incorporates measurements of IOP, episcleral venous pressure (22), and resistance to outflow. In measuring aqueous formation, it is noteworthy that an elevation of IOP will cause a decrease in aqueous humor formation; this pressure-sensitive process of aqueous humor formation is referred to as pseudofacility and is presumed to be the product of reduced ultrafiltration within the stroma of the ciliary body.

B. Outflow of Aqueous Humor

The outflow of aqueous humor from the eye in humans and primates occurs primarily through the "conventional" drainage pathway; that is, through the angle of

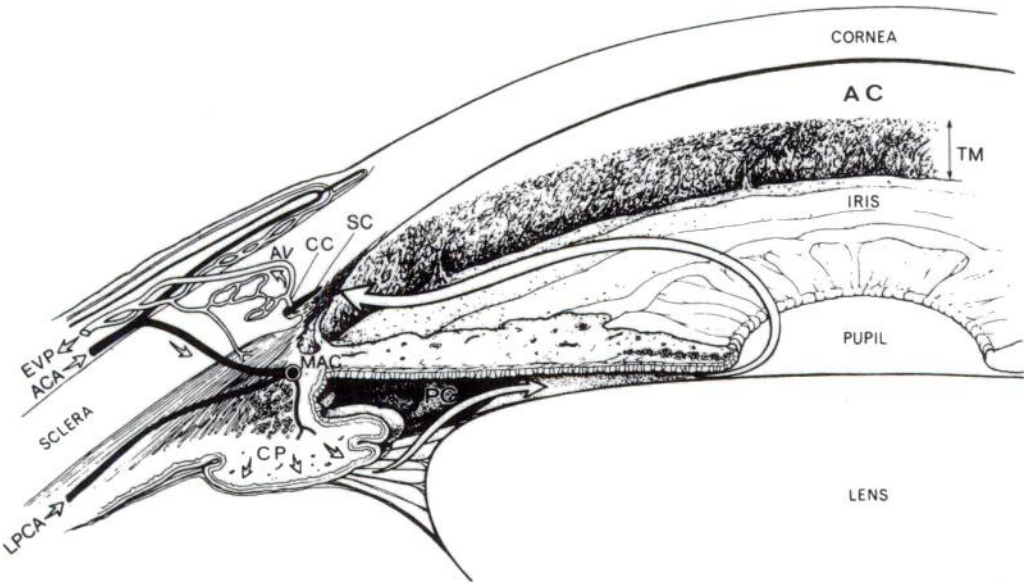

FIG. 1. Production, circulation, and drainage of aqueous humor. LPCA, long posterior ciliary artery; MAC, major arterial circle; CP, ciliary processes; PC, posterior chamber; AC, anterior chamber; TM, trabecular meshwork; SC, Schlemm's canal; CC, collector channel; AV, aqueous vein; EVP, episcleral venous plexus; ACA, anterior ciliary artery. (Reproduced with permission from W. J. Casey, *Clinical Ophthalmology*, vol. 3, ch. 45, 1978, J. B. Lippincott Co., Philadelphia).

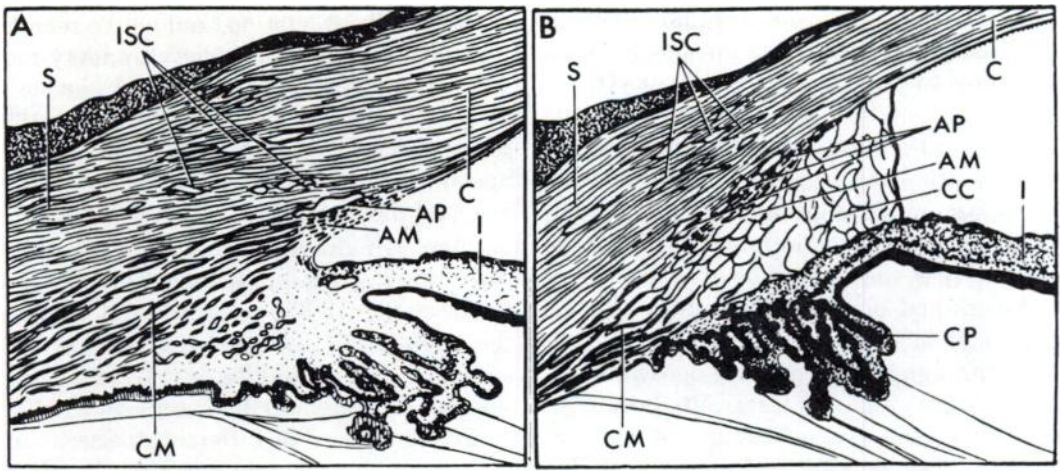

FIG. 2. Diagrammatic comparison of the iridocorneal angle of a primate (A) and a lower mammal (B) illustrating differences in morphological organization. S, sclera; C, cornea; I, iris; AM, angular meshwork; AP, angular aqueous plexus, CM, ciliary muscle; CC, ciliary cleft; CP, ciliary processes; ISC, intrascleral collector channels. (Reproduced with permission from R. C. Tripathi, *The Eye*, vol. 5, ch. 3, 1974, Academic Press, Inc., New York).

the anterior chamber, mostly by way of the trabecular meshwork, Schlemm's canal, intrascleral collector channels, aqueous veins, and the episcleral venous plexus. In the rabbit, aqueous humor drains through the ciliary cleft to an intrascleral plexus of veins and into the anterior ciliary veins; there is no well-defined trabecular meshwork system in most lower mammals (see fig. 2). An additional "unconventional" outflow pathway consists of the uveoscleral route, which may account for up to 20% of the aqueous humor outflow in primates (less in cats and negligible in rabbits) and is independent of IOP changes (10). In this accessory pathway, aqueous humor diffuses into the ciliary body and is carried away by the ciliary muscle veins, the suprachoroidal space, and the choroidal circulation.

The majority of resistance to outflow is assumed to reside in the outer trabecular meshwork and/or the inner wall of Schlemm's canal (or its equivalent in lower mammals). Glycosaminoglycans, consisting mainly of hyaluronic acid and the sulfated glycans, chondroitin-4-sulfate and dermatan sulfate, cover the meshwork and are believed to contribute to outflow resistance (121, 159). Outflow facility (C) is a measure of the ease or difficulty with which aqueous humor can leave the eye and is the reciprocal of resistance. The rate of aqueous outflow (F) is equal to C ($P_o - P_v$) where P_o is IOP and P_v is episcleral venous pressure. For convenience, a particular value is often assumed for P_v, but this can be measured by determining the pressure of a fine jet of air required to collapse the episcleral vessel (85). Measurement of facility of outflow can provide valuable information about the site and possible mechanism of action of drugs on IOP. The magnitude of resistance to outflow can be measured by determining turnover of fluorescein and other tracers in aqueous humor, by constant pressure perfusion of the anterior chamber (5), or by tonography (33). Tonography is a procedure, used experimentally and clinically, that measures the rate of decline in IOP caused by forcing fluid out of the eye by the addition of a weight to the tonometer probe. The total facility measured by tonography is made up of: 1) the facility of the trabecular meshwork/Schlemm's canal drainage system (true facility), and 2) the facility due to decreased aqueous secretion (pseudofacility) caused by an elevation in IOP (10).

III. Role of the Adrenergic Nervous System and Adrenoceptors in Modulating Aqueous Humor Dynamics

There is a relatively rich supply of autonomic nerves to the anterior uvea of the eye indicating that there is the potential for modulation of IOP by the autonomic nervous system (see section VI). It is believed that the sympathoadrenal transmitters and adrenergic drugs influence aqueous humor dynamics by effects on formation at the level of the ciliary blood vessels and ciliary epithelium and/or on outflow at the level of the trabecular meshwork, canal of Schlemm (intrascleral drainage channels in rabbits), ciliary smooth muscle cells, episcleral vessels, and/or intrascleral plexus. The ciliary body and processes, the iris, the choroid, and the intrascleral plexus appear to be innervated by sympathetic (adrenergic) neurons. In a phylogenetic study of 18 species, Staflova (177) found that structures in the posterior chamber, notably including the ciliary processes, had remarkably denser adrenergic innervation than the filtration area. In primates, the adrenergic innervation of structures in the anterior segment of the eye was found generally to be less dense.

It is somewhat paradoxical that drugs that affect function of the adrenergic nervous system and/or adrenoceptors in diverse ways can lower IOP; that is, IOP can be suppressed by drugs that either stimulate or inhibit adrenoceptor function. For example, both isoproterenol, a β-adrenoceptor agonist (141, 149), and timolol, a β-adrenoceptor antagonist (207), lower IOP. Modification of adrenoceptor function presumably results in a change in

aqueous humor formation and/or outflow and hence an alteration in IOP. Thus, there are several modes by which alteration of adrenoceptor function can modulate IOP: 1) by altering the rate of secretion (formation) of aqueous humor by the ciliary epithelium; 2) by changing the rate of ultrafiltration in the ciliary process secondary to changes in hydrostatic pressure gradient across the ciliary epithelium; 3) by modifying the outflow resistance (facility) either directly at the conventional outflow tract (trabecular meshwork and Schlemm's canal) or secondary to altered resistance in the episcleral veins; 4) by altering fluid flow through the uveoscleral pathway.

Linnér and Prijot (106) surgically interrupted the sympathetic innervation to the eyes of rabbits by cervical ganglionectomy and observed the consequence of this procedure on steady-state IOP. Twenty-four hours after cervical sympathetic ganglionectomy there was a transient decrease in IOP ipsilaterally. It was hypothesized that degenerating postganglionic sympathetic neurons released norepinephrine and that this resulted in decreased formation of aqueous humor. It has been postulated that uveal blood vessels have α-adrenoceptors but no β-adrenoceptors; this suggestion was supported by the demonstration that stimulation of noradrenergic neurons or topical application of epinephrine produces uveal vasoconstriction (8). However, it is highly likely that uveal vessels, especially arterioles, also have β_2-adrenoceptors. Increased activity of noradrenergic neurons to the blood vessels of ciliary processes in rabbits (54, 94) or topically applied epinephrine generally causes a reduction of aqueous formation (170); this is presumed to be an α-adrenoceptor-mediated effect. In contrast, acute β-adrenoceptor stimulation has been reported to increase aqueous humor formation in monkeys (11, 98) and humans (98, 187) but to decrease formation in rabbits (34) and in the arterially perfused cat eye (109). Sears and Bárány (163) demonstrated that resistance to outflow was about three times lower in the surgically sympathectomized eye of rabbits than in the normal eye. Subsequently, it was shown that the increase in outflow after ganglionectomy could be: 1) suppressed by previous depletion of norepinephrine stores by reserpine or α-methyl-*p*-tyrosine (150); 2) inhibited by prior administration of α-adrenoceptor antagonists (163); 3) reproduced by substances causing the release of norepinephrine and by intracameral injection of norepinephrine (165). Eakins and Ryan (36) showed that the increase in outflow facility after intravitreous norepinephrine or epinephrine was substantially inhibited by prior administration of phentolamine. Langham and Rosenthal (94) found that stimulation of preganglionic sympathetic nerves to the eye decreased the rate of aqueous humor formation but did not significantly influence the rate of drainage. It is interesting that Paterson (135) found that a significant increase in outflow facility in response to sympathetic nerve stimulation in the rabbit was produced only when reuptake of neuronally released norepinephrine was blocked with cocaine. Subsequently, it was demonstrated that phentolamine obtunded the increase in outflow facility elicited by cocaine-induced blockade of the reuptake of neuronally released norepinephrine (135). From these results, it has been inferred that one of the adrenoceptors responsible for increasing outflow in the rabbit eye is of the α-type.

There is marked species variation in the anatomy of the outflow tract, including adrenergic innervation (119) (see section VI). This may account for the differences in the ability of various adrenergic drugs to influence aqueous outflow in different species. Moreover, populations of various adrenoceptors may differ in the same ocular structures of different species. For example, responses to intracameral injections of adrenergic agonists have led to the suggestion that there are α- and β-adrenoceptor-mediated effects on outflow in the rabbit eye. One report indicated that injection of sympathomimetic amines after ganglionectomy increased outflow facility and decreased IOP in a dose-related way in the rabbit with the following order of activity: phenylephrine > norepinephrine > epinephrine > isoproterenol (165). In contrast, the primary adrenoceptor in the outflow tract in the eye of some primates has been suggested to be β (129, 131). Bill (9, 11) reported that outflow of aqueous humor from the eyes of vervet monkeys was increased by isoproterenol and epinephrine possibly due to an increase in uveoscleral outflow. Some workers have found that intracameral *d,l*-isoproterenol exerted no effect on total outflow in the eyes of Cynomolgus monkeys whereas epinephrine and norepinephrine increased outflow significantly (76). The maximum doses used in this latter study were 10 μg of *l*-epinephrine, *l*-norepinephrine, and *d,l*-isoproterenol. Therefore, the dose of *l*-isoproterenol delivered to the eye was approximately 5 μg, accounting perhaps for the inactivity of isoproterenol in this study.

From the preceding discussion it is clear that adrenergic mechanisms clearly influence aqueous humor dynamics in all species studied but that the response observed on formation and/or outflow of aqueous is highly variable between species. Anatomical differences in ocular structure and in morphology of adrenergic innervation are probably two of the main differences in species responsiveness to adrenergic manipulations. Variation in the distribution of adrenoceptors among those structures that regulate aqueous dynamics in various species is also an important determinant of response to adrenergic drugs.

IV. Action of Adrenergic Drugs

A. Potential Sites of Action

1. Intraocular and extraocular sites of action. There are two principal intraocular sites where adrenergic drugs are believed to produce lowering of IOP: the ciliary processes and the outflow tract. In addition to a poten-

tially direct effect on the secretory component of the ciliary processes, adrenergic drugs may exert a vasoconstrictor (α) action on afferent blood vessels of the ciliary process leading to a decrease in the rate of aqueous humor formation. If, as has been suggested, β-adrenoceptors are important in maintaining aqueous humor formation (184), then β-adrenoceptor antagonists could decrease aqueous humor formation by direct antagonism at sites in the ciliary epithelium or by augmentation of α-adrenoceptor function (vasoconstriction) in the blood vessels of the ciliary process.

The small caliber meshwork channels and the vessels (aqueous veins) in the outflow tract into which the aqueous humor eventually flows are potential sites of action for drugs. Resistance to outflow of aqueous humor resides in the communicating channel of the trabecular meshwork at the angle of the anterior chamber, Schlemm's canal, and aqueous veins, but the predominant adrenoceptors populating this part of the eye have been suggested to be α and/or β depending on the species (168).

When applied topically to the eye, adrenergic drugs may have multiple sites of action, including intraocular and extraocular. For example, topical timolol is widely distributed to extraocular tissue and levels decline to less than 10% of the maximum level in aqueous humor within four hours after instillation in the eyes of rabbits (160). Although generally considered to act locally on a variety of adrenoceptors in the eye, it seems possible, and in some cases highly probable, that certain topically applied adrenergic drugs may lower IOP through an action on the central nervous system (CNS). This mechanism has been proposed for timolol (100, 131) and may also be a possible site of action for clonidine (and similarly acting drugs) as well (100). The proposed CNS site of action for timolol is based on the observation that when the drug was given unilaterally it produced a lowering of IOP in the contralateral eye (145, 207). Since it was unlikely that the concentration reaching the contralateral eye was sufficient to produce lowering of IOP solely by a local effect, a potential central site of action was suggested (131). Moreover, studies in rabbits have shown that timolol penetrates structures of the eye less well than propranolol, which suggests that ocular penetration does not play a limiting role in the ocular hypotensive effect of β-adrenoceptor antagonists (148).

Cannabinoid drugs [Δ^9-tetrahydrocannabinol (THC), SP-1, and SP-106] caused a fall in IOP in intact, normal and in ganglionectomized eyes (56), indicating 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 seemed to have an effect on the CNS because ganglionectomy and preganglionectomy partially inhibited the fall in IOP produced by these drugs in rabbits.

2. Pre- and postjunctional receptors. Adrenergic agonists that lower IOP may act at pre- or postjunctional adrenoceptors. For example, clonidine at low to moderate doses seems to have a stronger action on α_2-adrenoceptors than on α_1-adrenoceptors. Although α_2-adrenoceptors are found at prejunctional sites, they may also be located postjunctionally as well. Postjunctional (postsynaptic) adrenoceptors are found in the pontomedullary region of the brain and stimulation by clonidine (or α-methylnorepinephrine) produces a fall in systemic arterial blood pressure (161).

After chronic sympathectomy in rabbits, Allen and Langham (2) demonstrated that clonidine failed to produce the fall in IOP that it produced in rabbits with intact superior cervical ganglia. Innemee and van Zwieten (71) reported that infusion of clonidine into the vertebral artery of cats produced a more pronounced fall in IOP than did i.v. injection. Thus, the centrally mediated effect of clonidine is presumed due to a general decrease of efferent sympathetic nerve activity to peripheral organs (83) and seems to be dependent on intact adrenergic innervation. In contrast, others have demonstrated that administration of the ganglionic blocker hexamethonium or the adrenergic neuron suppressants, guanethidine and bretylium, failed to antagonize the effects of clonidine on the eyes of cats (112). These latter results suggested that clonidine has direct effect(s) on ocular structures, in addition to its central action, to decrease aqueous humor formation and IOP in cats.

Drugs that act prejunctionally to alter sympathetic neuron function can lower intraocular pressure. Subconjunctival injection or topical administration of 6-hydroxydopamine causes chemical degeneration of sympathetic nerve terminals resulting in a transient decrease in IOP accompanied by temporary miosis (65). After chemical sympathectomy, there is increased responsiveness to adrenoceptor agonists postjunctionally (66, 67). One study has suggested that supersensitivity involves only α-adrenoceptor agonists (122) whereas other studies have indicated that there is increased postjunctional responsiveness to both α- and β-adrenoceptor agonists (26, 67). Thus, as in other systems, supersensitivity after 6-hydroxydopamine treatment probably involves both prejunctional (decreased reuptake) and postjunctional (increased receptor sensitivity) components. Guanethidine interferes initially with the release of norepinephrine caused by nerve stimulation and subsequently it interferes with storage of norepinephrine thereby depleting the neurotransmitter. This agent will produce a fall in IOP that has been attributed to an initial increase in outflow facility (179) followed by inhibition of aqueous humor secretion (16). Because guanethidine induces supersensitivity to adrenoceptor agonists, it also has been used in combination with epinephrine in treating open-angle glaucoma (136). Inhibition of norepinephrine synthesis by α-methyl-*p*-tyrosine can enhance the IOP-lowering effect of norepinephrine, isoproterenol, and epi-

nephrine in rabbits (26). These results suggest that pre- and postjunctional components of supersensitivity are involved in the development of increased responsiveness to adrenoceptor agonists after α-methyl-*p*-tyrosine.

Thus, adrenergic drugs may act directly on postjunctional adrenoceptors within the eye to influence IOP and/or they may also alter IOP by changing adrenergic neuron function either by actions on peripheral nerve endings or on sites within the CNS.

3. Localization of sites by receptor binding studies. The distribution of α- and β-adrenoceptors in the eye has not been studied extensively. Some investigations have shown that preparations of iris-ciliary body membranes from rabbit contain both α- and β-adrenoceptors as demonstrated by competitive binding between agonists and antagonists. Neufeld and Page (128) studied adrenoceptors in rabbit iris-ciliary bodies by measuring the binding of ^{3}H-dihydroergocryptine to α-adrenoceptors and ^{3}H-dihydroalprenolol to β-adrenoceptors. Clonidine, dopamine, and epinephrine were able to displace ^{3}H-dihydroergocryptine from the α-adrenoceptor whereas timolol, propranolol, isoproterenol, epinephrine, and norepinephrine inhibited the specific binding of ^{3}H-dihydroalprenolol to β-adrenoceptors. In this study, the agonist clonidine was more active than epinephrine and dopamine in displacing ^{3}H-dihydroergocryptine, indicating perhaps a predominance of α_2-type adrenoceptors in the iris-ciliary body preparation. Interaction at the β-adrenoceptor showed that isoproterenol was bound more avidly than epinephrine, norepinephrine, and dopamine; of interest was the observation that *d*-isoproterenol, a compound with minimal biological activity in most organs, was bound as avidly to the β-adrenoceptor as *l*-norepinephrine. An interesting in vivo finding was that *d*-isoproterenol, an active ocular hypotensive agent in rabbits, was relatively inactive in raising levels of cAMP (75, 155) and lactate (155) in aqueous humor of rabbits.

Dafna et al. (32) have also shown that β-adrenoceptors are numerous in certain parts of the rabbit eye. This study utilized the fluorescent analog of propranolol, 9-amino-acridin-propranolol (9-AAP) and demonstrated numerous β-adrenoceptors in the ciliary epithelium and episcleral vessels. Little or no 9-AAP fluorescence could be detected in the trabecular meshwork and only moderate fluorescence was observed in the iris sphincter. Based upon the distribution of 9-AAP binding sites, it was suggested that β-adrenoceptor agonists act mainly on the secretion of aqueous humor and to a lesser extent on the outflow tract. These latter results would suggest that β-receptor modulation of the outflow tract is minimal in the rabbit.

More recently Bromberg et al. (21) performed β-adrenoceptor ligand binding studies in rabbit ciliary processes exclusive of iridial or other uveal tissues. This group reported high-affinity binding sites for ^{125}I-hydroxybenzylpindolol (^{125}I-HYP) in particulate membrane fractions of homogenized ciliary processes. Adenylate cyclase activity was recovered in the same fraction as the ^{125}I-HYP binding sites. Beta adrenoceptor agonists (*l*-isoproterenol, *l*-norepinephrine) and antagonists (*l*-timolol, *l*-alprenolol, *d,l*-propranolol) displaced the radioligand from binding in this tissue. The results supported the suggestions that β-adrenoceptors are present in the ciliary processes of rabbits and that β-adrenergic drugs can modulate IOP by a direct interaction with the site for aqueous humor formation.

Mittag and Tormay (120) have investigated adrenoceptor subclasses in iris-ciliary body preparations from rabbits. These investigators demonstrated that the predominant subclass of β-adrenoceptors in this preparation was β_2 but that a large population of α_2-adrenoceptors was also present. The α_2-adrenoceptor population demonstrated more heterogenous antagonist specificity.

Another group (14) has shown that the predominant receptor population in cultured human trabecular cells is also β in character. These cells bound *l*-epinephrine to a greater extent than *d*-epinephrine. Timolol was shown to antagonize epinephrine-induced increases in cAMP in these cultured trabecular cells. β-Adrenoceptors were also shown to be present in bovine nonpigmented ciliary epithelial cells.

B. Potential Modes of Action

As alluded to previously, a wide variety of adrenergic drugs have been suggested to lower IOP at least in part by decreasing aqueous humor formation (25, 57). It is enigmatic that both agents with strong β-agonist or antagonist properties seem to be effective in reducing formation of aqueous humor (98, 200). The early traditional concept of adrenoceptor modulation of aqueous humor dynamics was that stimulation of β-adrenoceptors elicited a decrease in aqueous production and that stimulation of α-adrenoceptors in the outflow mechanism evoked an increase in facility of outflow (22, 93, 147). Although the traditional concept has been used to explain the effects of epinephrine, this hypothesis has been challenged recently because it fails to explain the pressure-lowering effect of timolol (184).

1. Adrenoceptor agonists. There are several mechanisms by which adrenergic agonists are proposed to lower IOP and these include: 1) a decrease in aqueous humor formation (or inflow) (35); 2) an increase in both true facility and pseudofacility (57); 3) an increase in uveoscleral drainage (9, 187); and 4) a decrease in episcleral venous pressure, although a sustained effect on this parameter has not been found (171).

A. EPINEPHRINE. According to Sears (171), the early effects of epinephrine on aqueous formation and outflow are due to α-adrenoceptor effects. The reduced formation (or inflow) was postulated to be due to stimulation of α-adrenoceptors in the vessels of the ciliary stroma. The main reduction in blood flow by epinephrine in monkeys occurs in the ciliary process as determined by the distribution of labeled microspheres (3). The resulting vaso-

constriction is presumed to reduce ultrafiltration in the ciliary processes. The early and intermediate effects of epinephrine on outflow facility were believed by Sears (131) to be related to a β-adrenoceptor effect and the generation of cAMP. The increased outflow of aqueous humor could be the product of stimulating trabecular cells and/or perhaps altering function of endothelial cells of Schlemm's canal or smooth muscle cells in the ciliary body. However, β-adrenoceptor stimulation of ciliary smooth muscle cells generally causes relaxation, and this effect should not result in an increase outflow of aqueous humor. It should be noted that a very early increase in gross outflow facility, as measured by tonography in the rabbit, may be apparent in part because epinephrine may increase IOP resulting in an increase in pseudofacility; that is, a decrease in the pressure-dependent part of inflow. The late-occurring decrease in resistance to aqueous outflow produced by epinephrine has been postulated by Sears (169) to be due to a change in the nature of glycosaminoglycans in the trabecular meshwork.

Studies of epinephrine in the eyes of normal, nonglaucomatous humans suggested that the effects of epinephrine differ with the dose (96). Low concentrations of epinephrine decreased IOP without effects on outflow facility and pupil diameter; the hypotensive effect presumably was due to decreased formation of aqueous humor. Increases in outflow facility, mydriasis, and decreased IOP were observed at higher concentrations.

More recently, it has been shown that the acute effect of epinephrine in the normal human eye is to lower IOP, to increase tonographic facility of outflow, and to increase the rate of loss of fluorescein from the anterior chamber (187). The latter effect was concluded to be due to a more rapid washout of fluorescein caused by an increased rate of formation of aqueous humor; however, diffusional loss or loss of fluorescein via the corneal epithelium or through the lens and posterior chamber could not be excluded totally. It was pointed out in this study that the acute (single dose) effect of epinephrine in normal eyes may differ from the effects of chronic administration or may differ from the effects in patients with abnormal aqueous humor dynamics.

Another recent study from the laboratory of Brubaker (63) has shown that acute topical administration of epinephrine on normal eyes pretreated with the β-adrenoceptor antagonist timolol maleate lowered aqueous formation as demonstrated by a decrease in rate of fluorescein loss from the anterior chamber. Thus, the authors suggested that timolol antagonized the stimulatory (β) effects of epinephrine on aqueous humor formation. Although the combination of timolol and epinephrine decreased aqueous humor flow more than either timolol or epinephrine alone, there was no significant difference in IOP. The further decrease in aqueous production (flow) by epinephrine in the presence of timolol also could have been due to enhanced α-adrenoceptor activity as the result of β-adrenoceptor blockade.

Long-term epinephrine treatment in humans tends to lower aqueous humor formation as well as increase outflow (170). These time-dependent effects of epinephrine with chronic administration could be in part due to nerve terminal degeneration (43) or to reduction in the number and/or sensitivity of β-adrenoceptors in ocular structures (86, 130). This latter effect in the ciliary body would be presumed to decrease aqueous formation and in effect would be similar to β-adrenoceptor antagonism.

B. DIPIVALYL EPINEPHRINE. Dipivalyl epinephrine (DPE, dipivefrin HCl) represents an epinephrine analog that differs from the parent compound by the addition of two pivalic acid groups to the hydroxyl groups on the aromatic ring (115). This modification makes DPE more lipophilic than epinephrine and qualifies DPE as a prodrug; that is, an agent that undergoes biotransformation to the parent compound before exhibiting its pharmacological action. It has been shown that esterases presumably in the cornea and aqueous humor biotransform DPE to epinephrine. As a result of its greater penetrability, DPE is effective at very low concentrations (0.025%). Although its spectrum of pharmacological action in the eye is the same as epinephrine, this prodrug is absorbed more completely, is more potent, and should have a reduced incidence of ocular and systemic toxicity as a result of a lower effective dose.

C. NOREPINEPHRINE. Norepinephrine is similar to epinephrine in that it also elicits an initial rise followed by a depression in IOP in rabbits (141, 195). It was proposed by Sears and Sherk (165) that norepinephrine lowered IOP in the rabbit by acting directly on the intrascleral trabecular canals. Pollack and Rossi (139) found that norepinephrine produced a significant decline in IOP and total resistance to outflow in human subjects with glaucoma. Although these studies indicated a primary action on the outflow tract, several groups (57, 94, 110) have also suggested that norepinephrine can also decrease formation of aqueous humor in rabbit and cat eyes.

D. DOPAMINE. Dopamine caused a modest dose-related decrease in IOP in rabbits either directly through an action on dopamine receptors or possibly indirectly through the release of norepinephrine. Since haloperidol inhibited the ocular hypotensive effect of dopamine, it was suggested that the principal effect was on dopamine receptors (174). However, it should be noted that in sufficient doses haloperidol will also antagonize α-adrenoceptor stimulation. Several studies have concluded independently that the major effect of dopamine on aqueous dynamics is suppression of aqueous formation (111, 174). Dopamine was similar to other adrenoceptor agonists with α-activity in that it produced an initial ocular hypertensive effect when applied topically to the eyes of rabbits (141).

E. PHENYLEPHRINE. Phenylephrine, a relatively selective α_1-adrenoceptor agonist, can produce a biphasic effect on IOP in rabbits; that is, an initial rise in IOP followed by a modest, late-occurring fall (141). One group

has suggested that phenylephrine can decrease total outflow facility (57) whereas another indicated that phenylephrine can decrease aqueous humor formation (111).

F. ISOPROTERENOL. Isoproterenol, a nonselective β agonist, has been reported to affect both inflow (35) and outflow (98) of aqueous humor from the anterior chamber in rabbits and thus to lower IOP. Eakins (35) injected isoproterenol into the vitreous and found that aqueous humor formation was depressed. The effect was attributed to a decrease in blood flow to the ciliary processes or to direct effects on metabolic processes involved in secretion. Although the action of isoproterenol is considered to be direct, it was suggested by Macri (109) that isoproterenol has a ganglion-stimulating effect in the perfused cat eye and that this resulted in the release of nonepineprhine. In rabbits, isoproterenol was reported to decrease outflow facility in one case (133) and to increase it in another (98). This discrepancy may reflect a different effect on ocular function based upon the site of administration and/or dose administered. In high doses, isoproterenol stimulates β- and α-adrenoceptors. When isoproterenol was perfused through the anterior chamber of vervet monkeys, it increased aqueous humor production, total outflow facility, and rate of uveoscleral drainage (11). When used by acute topical administration in rabbits at a concentration of 2%, both the *d*- and *l*-isomers of isoproterenol produced significant hypotension in the ipsilateral (treated) and contralateral (fellow) eyes (141); the transient, contralateral effect diminished as the dose was decreased. The latter observation suggests that isoproterenol either is being distributed to the contralateral eye by the blood or that a consensual effect is being produced by some other mechanism. Repeated (on consecutive days) high doses of *l*-isoproterenol and other β-agonists can produce ocular hypertension in rabbits (99, 142) (see section V).

l-Isoproterenol will lower IOP in all species, but its clinical utility is limited by ocular hyperemia and development of tolerance to the pressure-lowering effect (149). *d*-Isoproterenol seems to be active only in the rabbit (75, 155, 173). Gaasterland et al. (47) showed that isoproterenol lowered both IOP and secretory rate in normal subjects but had no effect on facility of outflow or episcleral venous pressure. Isoproterenol also lowered pressure in glaucomatous subjects (149, 199).

G. RELATIVELY SELECTIVE β-AGONISTS. Drugs with greater selectivity for β_2-adrenoceptors, such as salbutamol, terbutaline, soterenol, and reproterol, have been shown to lower IOP in rabbits (141, 155), in monkeys (98), in cats (27), and in humans (136, 201) with acute topical application. β-Agonists that are relatively selective for β_1-adrenoceptors are weakly active ocular hypotensive agents in the rabbit (141). Topical and i.v. administration of salbutamol increased total outflow facility slightly and decreased formation of aqueous humor and IOP in rabbits and monkeys (98); however, in other studies terbutaline did not increase outflow facility.* Wettrell et al. (201) reported that orally administered terbutaline lowered IOP in humans, but no suggestion was made regarding mechanism of action.

Relatively selective β_2-agonists may not have purely agonistic actions in the eye. For example, it should be noted that salbutamol is a partial agonist at β-adrenoceptors in at least two other sites in body, the kidney (202) and the cerebral cortex (118). For example, in the cerebral cortex of rats, salbutamol is an agonist at β_2-receptors and a potent antagonist at β_1-receptors. It is interesting that with chronic treatment in the eye, salbutamol did not produce ocular hypertension in the rabbit as readily as isoproterenol.* Thus, partial agonists, such as salbutamol, may be capable of stimulating some β-adrenoceptors in the eye while antagonizing others. In the case of chronic treatment, salbutamol could be upregulating (increasing number or sensitivity) β_1-adrenoceptors while down-regulating (decreasing number or desensitizing) β_2-adrenoceptors. This raises the probability that innervated β-adrenoceptors (β_1) may be regulated independently from noninnervated (hormonal) β-adrenoceptors (β_2) in the eye.

H. BIOCHEMICAL MODE OF ACTION OF β-ADRENERGIC DRUGS. Waitzman and Woods (194) first reported that catecholamine-stimulated adenylyl cyclase was present in the ciliary processes of the rabbit. More recently, Nathanson (125) found that β-adrenoceptors in the isolated ciliary process epithelium in rabbits have characteristics of β_2-adrenoceptors. The order of adrenergic agonist activity on adenylyl cyclase in this preparation was isoproterenol > epinephrine > norepinephrine > phenylephrine. Of the relatively selective β-agonists tested, the β_2 agonists zinterol and OPC 2009 showed greater activity than isoproterenol whereas prenalterol, a selective β_1-agonist, was virtually ineffective. The relatively selective β_2-antagonist IPS 339 was as potent as the nonselective agents propranolol and timolol in inhibiting isoproterenol-stimulated adenylyl cyclase activity in ciliary epithelial cells from rabbits. These data were interpreted to mean that the β_2-adrenoceptor is associated with the ciliary process in the rabbit and that relatively selective β_2-antagonists should be as effective as nonselective β-antagonists in lowering IOP. Thus, in vitro (125) and in vivo (141) data strongly support the suggestion that the β_2-adrenoceptor is an important pharmacological site for regulation of aqueous humor production and IOP in the ciliary process of the rabbit.

As in other tissues, β-adrenoceptor activity in the eye can be mediated through the activation of adenylyl cyclase with the resultant formation of cyclic AMP. It has been shown that the decrease in IOP caused by β-adrenoceptor agonists in rabbits generally parallels the rise in cAMP concentration (127). It is interesting that nei-

* Potter and Rowland, unpublished observations.

ther the isoproterenol-induced elevation in cAMP nor the decrease in IOP were inhibited by propranolol in this study. Since the antagonist propranolol was administered systemically (i.v.), it is highly likely that insufficient antagonist reached the eye relative to the amount of topically applied agonist. In a more recent study of nonselective β-agonists in rabbits, it was reported that the increase in cAMP in aqueous humor was not necessarily directly related to the agent's hypotensive activity (151). The order of activity in elevating cAMP levels in treated eyes was: epinephrine = isoproterenol > terbutaline > phenylephrine = tazolol. Although terbutaline raised cGMP levels in this study, none of the other agents demonstrated this capacity. A dissociation between hypotensive activity and cAMP generation was also shown in a study comparing *d*- with *l*-isomers of epinephrine, norepinephrine, phenylephrine, isoproterenol, and soterenol (155). The *d*-isomers were as active, and in some cases more active than, the *l*-isomers in terms of lowering IOP in rabbits, but *d*-epinephrine, *d*-phenylephrine, *d*-isoproterenol, and *d*-soterenol had only 15% to 25% of the activity of the respective *l*-isomers in raising cAMP levels. These results indicated that *d*-isomers of the β-agonists can lower IOP in rabbits by some receptor mechanism other than one dependent on the generation of cAMP.

2. *Adrenoceptor antagonists.* Both α- and β-adrenoceptor antagonists lower IOP but presumably by different mechanisms. α-Adrenoceptor antagonists have been shown to lower normal and elevated IOP in animals and humans. Phenoxybenzamine (55, 97), dibenamine (163), thymoxamine (136), and phentolamine (55, 97) lowered IOP and produced an increase in total outflow facility in rabbits. In contrast, one group has reported a decrease in IOP produced by phentolamine accompanied by a decrease in total outflow facility in humans (31). β-Adrenoceptor antagonists are presumed to lower IOP principally by decreasing aqueous humor formation.

A. THYMOXAMINE. The α-adrenoceptor antagonist thymoxamine has received considerable attention as a potential diagnostic and therapeutic agent in glaucoma (157). Because of its α-adrenoceptor antagonism in the dilator pupillae, thymoxamine has been used to reverse phenylephrine-induced mydriasis during examination of the fundus (116) and to treat angle-closure glaucoma (58). In theory, the miosis produced by thymoxamine should be advantageous in that it would evoke less posterior vector force than parasympathomimetic agents at the pupil because of its lack of effect on the ciliary muscle. Rutkowski et al. (157) found that thymoxamine, 0.5% alone every minute for five minutes and then every 15 minutes for up to three hours, interrupted an attack of angle-closure glaucoma. Thymoxamine has also been proposed for use in differentiating angle-closure glaucoma from open-angle glaucoma complicated by narrow angles (198). The advantage of thymoxamine over other drugs is related once again to its lack of effect on the ciliary muscle. In relieving acute angle-closure glaucoma in humans, thymoxamine lowers IOP presumably by overcoming mydriasis and pupillary block (157). A study demonstrated that 2.5% thymoxamine topically did not lower normal IOP in rabbits but 5% thymoxamine produced a delayed but transient drop in IOP (92).

B. RELATIVELY SELECTIVE α-ANTAGONISTS. More recent evidence has shown that other antagonists with relative selectivity for subpopulations of α-adrenoceptors will lower IOP. For example, yohimbine, relatively selective for α_2-receptors, (124) and prazosin, relatively selective for α_1-receptors (154, 176), both lowered normal IOP in rabbits.

C. PROPRANOLOL. Sears and Bárány (163) applied dichloroisoproterenol to the eyes of rabbits and found that this partial β-adrenoceptor agonist lowered IOP and increased total outflow facility. Subsequently, the β-adrenoceptor antagonist propranolol, when administered i.v., was reported to lower IOP within one hour in patients with glaucoma (137). Further clinical investigation with other routes of administration corroborated the ocular hypotensive action of propranolol (41, 175, 189, 190). Originally it was thought that the local anesthetic activity of propranolol was responsible for its lowering of IOP; however, this has been discounted as the probable mechanism because practolol, a relatively selective β_1-adrenoceptor antagonist without significant local anesthetic activity, also lowered IOP (191). Topical administration of propranolol proved to be of limited therapeutic utility because of its strong local anesthetic activity and tendency to produce ocular irritation (200). It has been reported that propranolol increased outflow facility in rabbits (55) and in glaucomatous humans (181) whereas others have reported that propranolol decreased facility of outflow (182, 186) but inhibited formation of aqueous humor in humans (182). Hence, although propranolol can lower IOP, the effect of outflow facility was affected variously, but formation of aqueous humor was depressed. Episcleral venous pressure was reported by Wettrell (200) to be unaffected by propranolol.

D. TIMOLOL. Timolol is a nonselective β-adrenoceptor antagonist that is 5 to 10 times more potent than propranolol (162) and is relatively devoid of sympathomimetic and local anesthetic properties (59). Katz et al. (76) reported that single administration of 0.5%, 1.0%, and 1.5% timolol produced decreases in IOP in the normotensive eyes of human volunteers. Subsequently, Zimmerman and Kaufman reported that topically applied timolol lowered IOP approximately 50% (207) with no significant effect on outflow facility (208). Based upon the latter finding, the suggestion was made that timolol lowered IOP by decreasing formation of aqueous humor. A fluorophotometric study of the effect of topical timolol in normal patients and patients with ocular hypertension demonstrated that the acute decrease in IOP was accom-

panied by a 48% decrease in aqueous flow (205). Coakes and Brubaker (25) assessed the effect of timolol in 23 normal subjects and showed suppression of aqueous humor formation in all subjects with no effect on outflow resistance. It has been noted that, while on chronic therapy with timolol, a patient's IOP may undergo short term "escape" and long term "drift" (15). The former phenomenon is used to indicate an acute partial loss of therapeutic effect on IOP during the first few days of timolol treatment. Other individuals have shown slow upward trend in IOP after months of therapy. These phenomena may be related to a change in the density of β-adrenoceptors during chronic therapy with timolol. In this regard Neufeld and coworkers (130) have demonstrated that there is a decrease in β-adrenoceptors in ocular tissues from rabbits with continuous timolol therapy; however, the change in number of receptors was not correlated directly with a change in the physiological response of the cell. Moreover, one might suspect that the number of β-adrenoceptors would be increased after chronic therapy with a β-adrenoceptor antagonist (52).

Timolol produced dose-dependent lowering of IOP in several species (19, 27) and suppression of aqueous formation in cats (107) and in humans (205), but the ocular hypotensive effect in rabbits is much more controversial (131, 145, 192). The controversy concerning the activity of timolol in the rabbit eye may be related to anatomical features peculiar to this species, or it may reflect the established diurnal (146) and seasonal (193) variation of IOP in the rabbit. Cyclic variations in IOP in the rabbit and other species may be related in part to variations in hormonal influences as well as fluctuations in sympathoadrenal function.

In comparison to man, the doses of timolol required to lower IOP in the cat were relatively large (27). The ocular hypotensive effect of timolol in the cat was markedly reduced after sympathetic denervation, indicating the probable influence of active sympathetic tone on aqueous humor production. The enucleated perfused cat eye failed to respond to timolol alone although timolol did inhibit the effects of isoproterenol (113). This also suggests that active sympathetic tone must be present to observe the suppressive effect of timolol on IOP.

Topical treatment with timolol not only decreased IOP but also decreased tear production in glaucoma patients; the inhibition of tear formation was limited quantitatively and was not deemed dangerous unless the eye in question had abnormally low lacrimal secretion (20). Other β-adrenoceptor antagonists, both relatively β_1 selective (metoprolol) and nonselective (propranolol), have been shown to antagonize tear flow in rabbits induced by isoproterenol and the selective β_1-agonist H 80/62 (1).

E. OTHER β-ANTAGONISTS. Other nonselective (butidrine, pindolol, oxprenolol, sotalol) and relatively selective β_1 (atenolol, practolol, metoprolol) adrenoceptor antagonists have been studied in animals and in humans, and all have been reported to lower IOP to varying degrees. In a comparison of nine β-adrenoceptor antagonists (practolol, timolol, sotalol, pindolol, oxprenolol, propranolol, butidrine, metoprolol, and atenolol) in the rabbit, timolol and sotalol demonstrated the greatest potency and duration of action of the group (19). Pindolol, oxprenolol, practolol, and propranolol were of intermediate potency whereas atenolol, butidrine, and metoprolol were the least active of the group. The conclusion drawn from this study was that selectivity for β_1- or β_2-adrenoceptors did not seem to be a primary determinant of a β-adrenoceptor antagonist's ability to lower IOP.

Atenolol, a relatively selective β_1-antagonist, was ineffective in cats (27) although it reportedly had ocular hypotensive effects in humans (138). A human study utilizing atenolol led to the suggestion that the reason why both β_1 blockade and β_2 stimulation reduced ocular tension was that the net effects of β_1- and β_2-adrenoceptor function on aqueous dynamics are opposite; that is, that β_1 agonistic effects tend to increase IOP whereas β_2 agonistic effects tend to decrease IOP (40). A subsequent clinical study tested the possibility that β_1 stimulation caused ocular hypertension and that α- and β_2-agonistic actions produced ocular hypotensive effects (138). The study showed that the ocular hypotensive effects of atenolol (relatively selective β_1-antagonist)-then-adrenaline (α-, β_1-, β_2-agonist) were not different from adrenaline-then-atenolol. Atenolol alone was significantly better than atenolol followed by adrenaline whereas adrenaline alone was no better than the combined therapies. These data would seem to indicate that adrenoceptor activation by adrenaline antagonized the ocular hypotensive effect of atenolol in humans. Moreover, the results with atenolol alone can be interpreted to mean that the β_1-adrenoceptor may also be important in promoting aqueous humor formation in the human. Additional studies with relatively selective β_2-adrenoceptor antagonists might aid in determining the degree of β-adrenoceptor control of aqueous humor dynamics in humans.

Two relatively selective β_2-antagonists, H 35/25 and IPS 339, have been shown to lower IOP in cats (27) and rabbits (126), respectively. The ocular hypotensive effect of H 35/25 was less in sympathetically denervated cat eyes. The effect of IPS 339 in the rabbit was similar in magnitude to timolol and, like timolol, the effect was modest and bilateral. It was assumed that the fall in IOP to IPS 339 was due to decreased aqueous humor production.

F. LABETALOL. Labetalol is a unique adrenoceptor antagonist in that both α- and β-adrenoceptor functions are inhibited although β-adrenoceptor inhibitory effects seem to predominate (42, 79). This drug would seem to be potentially useful in the treatment of both narrow-angle and open-angle glaucoma. It has been shown that this agent lowered IOP in rabbits in a dose-related manner (123). It was suggested in this report that labetalol had no effect on the coefficient of aqueous outflow facil-

ity, indicating that labetalol must have decreased formation of aqueous humor. Additional studies in rabbits have shown that the ocular hypotensive response to labetalol was not as pronounced after cervical sympathectomy and subsequent degeneration of sympathetic nerve endings (104). These results suggested that intact sympathetic nerve endings are necessary for maximal ocular hypotensive activity of labetalol and that labetalol may act in part by inhibiting the reuptake of norepinephrine (42, 79). Pretreatment with timolol, which by itself did not produce a fall in IOP, obtunded the drop in IOP evoked by labetalol, suggesting a similar site of action. In the same study, the authors stated that labetalol was ineffective as an inhibitor of the ocular hypotensive effect of isoproterenol leading to the suggestion that labetalol did not decrease IOP solely by β-adrenoceptor blockade. However, it is difficult to draw this conclusion because both agents (labetalol and isoproterenol) produced ocular hypotension in rabbits at the doses used in this portion of the study.

3. Drugs that can alter adrenergic neuron function.

A. CLONIDINE. Makabe (114) observed a reduction in IOP after the i.v. and oral administration of clonidine and suggested that the effect was due to inhibition of aqueous humor secretion. Later, Hasslinger (61) reported that local application of an 0.5% aqueous solution of clonidine produced a reduction in IOP in patients with glaucoma. The undesirable signs and symptoms of lowered systemic arterial pressure, xerostomia, and tiredness led these investigators to suggest that the drug was absorbed systemically and that a central sympatholytic action of the drug became manifest. There was a demonstrable improvement in outflow facility that was attributed to a contraction of the meridional segment of the ciliary muscle that in turns acts on the scleral spur to increase flow through the trabecular structure. Although accommodation and pupillary diameter were unaffected in these patients, there was a reported change in refraction suggesting that adrenergic neuronal input to the ciliary muscle was affected by clonidine. Subsequently, another experimenter reported that 0.25% of clonidine topically produced less pronounced effects on IOP and arterial pressure. Sayegh et al. (158) proposed that the lowering of IOP by clonidine was secondary to a decrease in systemic blood pressure. However, an argument against this suggestion was the difference in temporal response and the fact that topical application of clonidine (0.125%) lowered IOP but did not decrease opthalmic arterial pressure (87). A study utilizing patients with normal and glaucomatous eyes demonstrated that threshold doses of clonidine induced a monotonic, unilateral decrease in IOP (88). As the dose of topical clonidine was increased, a pressure-lowering effect was observed in the contralateral (untreated, fellow) eye, and there was also a decrease in systemic arterial pressure. Episcleral venous pressure decreased in both treated and untreated eyes, but the drop was considered insufficient to account for the decline in IOP. The conclusion drawn from this study was that the ocular hypotensive effect of clonidine is mediated by inhibition of central and peripheral adrenergic neuronal activity of the eye.

Clonidine, at lower doses, interacts principally with α_2-adrenoceptors and in doing so elicits mydriasis and a biphasic change (elevation then depression) in IOP in experimental animals (2, 88). Studies in monkeys and cats have substantiated the effects of clonidine on aqueous humor dynamics (13). In anesthetized monkeys, clonidine decreased outflow facility slightly but had little effect on IOP and formation of aqueous humor. In anesthetized cats, clonidine suppressed ocular blood flow and decreased intrascleral venous pressure, which was attributed to local vasoconstriction. With a perfused iris-ciliary body preparation obtained from cats, Macri and Cevario (112) were able to demonstrate that clonidine (0.1 μg/ml) produced a direct effect on the eye to decrease aqueous humor formation and IOP. It was suggested that clonidine, like phenylephrine and dopamine, decreased aqueous humor formation by a direct vasoconstrictor action on afferent blood vessels in the ciliary process.

Topically applied clonidine was reported to lower IOP in the treated but not the untreated eye of anesthetized rabbits (64). However, in additional studies on rabbits, a biphasic IOP response (brief rise followed by a prolonged fall) was observed to topically applied clonidine in treated eyes and a monophasic lowering of IOP was observed in contralateral eyes (88). Intravenously administered clonidine elicited a monophasic lowering of IOP. Prior i.v. administration of phenoxybenzamine inhibited the rise in IOP and the slight increase in pupil diameter to topically applied clonidine, indicating to the authors that stimulation of ocular α-adrenoceptors had occurred. Interestingly, antagonists of cholinergic (nicotinic) transmission at the neuromuscular junction also antagonized the ocular hypertensive effect of clonidine in rats, suggesting that contraction of extraocular muscles was responsible for the transient increase in IOP (70). The hypotensive response to clonidine was suggested to occur in the central nervous system in that it was dependent on intact sympathetic innervation of ocular tissues, that is, clonidine was ineffective in lowering IOP in treated eyes after unilateral cervical preganglionic sympathectomy whereas IOP was lowered in the contralateral eyes where sympathetic innervation was intact (88).

B. 6-HYDROXYDOPAMINE. The basis for the combined use of pharmacological denervation and epinephrine in the treatment of glaucoma originated with studies of patients with Horner's syndrome. Swegmark (180) investigated, in detail, aqueous humor dynamics in a patient with unilateral Horner's syndrome. Subsequently, based upon results obtained with epinephrine in denervated rabbit eyes (164), Sears (166) treated 19 patients with Horner's syndrome with epinephrine. It was noted that the factors controlling outflow facility were supersensitive to the effects of epinephrine. These studies laid the

groundwork for the rational combination of chemically induced supersensitivity (6-hydroxydopamine, α-methyl-*p*-tyrosine, guanethidine) and epinephrine in the treatment of refractory glaucoma.

6-Hydroxydopamine is an analog of norepinephrine that has an additional hydroxyl on the aromatic ring and no hydroxyl group on the β-carbon. Topical administration or subconjunctival administration of 6-hydroxydopamine in humans evoked a transient decrease in IOP accompanied by a biphasic change in pupil diameter, mydriasis followed by temporary miosis (68). These effects are the result of a relatively selective destruction of noradrenergic nerve endings (188). This chemical sympathectomy produced supersensitivity to the IOP-lowering effect of adrenergic amines (65, 66). One study has suggested that the supersensitivity developed only to α-adrenoceptor agonists (122). In contrast, other investigators claimed that the supersensitivity to ocular hypotensive effects developed to both α- and β-adrenoceptor agonists (26, 67). The results of these studies suggested that supersensitivity after treatment with 6-hydroxydopamine probably involved both prejunctional (altered reuptake) and postjunctional (altered effector) mechanisms. Nonspecific mechanisms other than specific changes in receptor density may be involved in postjunctional supersensitivity. For example, Page and Neufeld (134) reported that chronic sympathetic denervation caused no increase in the affinity or numbers of adrenoceptors in the rabbit iris. Clinically, chemical sympathectomy by itself is of little or no therapeutic benefit, but when combined with topically applied epinephrine, it can be used to treat open-angle glaucoma in patients on maximum medical therapy and other glaucomas, such as hemorrhagic glaucoma or that secondary to uveitis (68).

C. α-METHYL-*p*-TYROSINE. Interruption of the rate-limiting step in catecholamine biosynthesis by α-methyl-*p*-tyrosine has been tried as a means of lowering IOP. Colasanti and Trotter (26) administered α-methyl-*p*-tyrosine i.p. twice daily for seven days to rabbits and found that the ocular hypotensive actions of epinephrine, norepinephrine, and isoproterenol were enhanced. However, the activity of norepinephrine was enhanced more than that of the other two catecholamines. Postjunctional supersensitivity was suggested as the apparent mechanism involved in the enhanced response to exogenous catecholamines after depletion of tissue catecholamines by α-methyl-*p*-tyrosine.

D. GUANETHIDINE. Guanethidine is a drug that interferes with adrenergic neuron function initially by inhibiting the release of norepinephrine by the action potential and subsequently by depleting norepinephrine from storage granules. Topical administration of guanethidine produced a fall in IOP that was transient (78) and attributed to an initial increase in outflow facility (179) followed by inhibition of aqueous humor production (16). Guanethidine has also been used concurrently with epinephrine; the rationale for this combination therapy is based upon the production of guanethidine-induced supersensitivity. In one study it was reported that the combination of 5% guanethidine and 1% epinephrine was more effective than guanethidine alone in lowering IOP in humans (136). In one human study, as the length of the combined therapy progressed, a biphasic effect on IOP was observed (69).

4. Other inhibitors of catecholamine disposition.

A. INHIBITORS OF MONOAMINE OXIDASE (MAO) AND CATECHOL-O-METHYLTRANSFERASE (COMT). It has been suggested that the two principal enzymes responsible for the degradation of catecholamines, namely monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT), may have a role in aqueous humor dynamics. Studies in rabbits have shown that both enzymes are present in various structures of the eye including retina-choroid, iris-ciliary body, optic nerve, and extraocular muscles (197). The MAO inhibitor nialamide lowered IOP and blood pressure in rabbits when administered i.v. (183). Zeller et al. (206) reported that MAO inhibitors potentiated the effects of epinephrine and isoproterenol on IOP, outflow facility, and aqueous humor flow in the rabbit eye. Moreover, these researchers suggested differential effects of A and B MAO inhibitors on adrenergic responses of the iris. Pargyline was shown to decrease IOP in the normal rabbit eye but not in the denervated eye, which suggests that the effect of this drug was dependent upon intact adrenergic innervation (6). Pargyline has also been shown to lower IOP in glaucoma patients (117).

Inhibition of COMT by 3′,4′-dihydroxy-2-methylpropiophenone was shown to potentiate the effects of topically applied epinephrine on mydriasis and outflow pressure in the denervated eyes of rabbits (7). Under certain circumstances, COMT activity becomes important in regulating the ocular response to catecholamines: 1) when nerve uptake mechanisms are suppressed by drugs (72), and 2) when the nerve terminals degenerate such as occurs in the trabecular region in open-angle glaucoma (204), in the human aging process (89), and during chronic therapy with epinephrine (43).

B. UPTAKE INHIBITORS. Blockade of neuronal reuptake of norepinephrine with cocaine caused a significant increase in outflow facility to electrical stimulation of the preganglionic cervical sympathetic nerve in the rabbit (135). Later, Langham and Carmel (95) suggested that other inhibitors of norepinephrine reuptake should enhance the effects of neuronally released and exogenously applied norepinephrine on aqueous humor dynamics. It was demonstrated in rabbits, monkeys, and humans that tricyclic compounds such as protriptyline could exert significant potentiation of IOP responses to sub- and supramaximal rates of electrical stimulation and to exogenously applied norepinephrine. As an extension to their earlier study, Kitazawa and Langham (82) demonstrated that protriptyline prolonged the ocular hypoten-

sive response to norepinephrine whereas the prolongation of the effect was less for epinephrine and negligible for isoproterenol. These results agree with the concept that epinephrine and norepinephrine undergo reuptake by adrenergic nerve endings but that isoproterenol is not taken up appreciably.

V. Ocular Hypertensive Effects of Adrenergic Agonists

Henderson and Starling (62) observed a slight rise followed by a fall in IOP after stimulating the sympathetic nerves to the eyes of dogs and cats; in rabbits the initial rise was not observed. These findings were interpreted to be due to differences in the presence and amount of sympathetically innervated smooth muscle (Müller's muscle) in the orbit of the eyes of the different species. Later, Eakins and Katz (37) demonstrated that stimulation of the cervical sympathetic nerve in the cat resulted in increased tension of the extraocular muscles and a transient increase in IOP. These effects could be potentiated by blocking norepinephrine reuptake with cocaine. At about the same time, it was reported that transient increases in IOP as great as 10 mm Hg can be evoked in the rabbit eye by low intensity sensory stimulation (29). This evoked hypertensive IOP response was postulated to be produced by sympathetically induced contraction of the orbital smooth muscle of Müller and was believed to be mediated by an α-adrenoceptor because phentolamine inhibited this response.

Although adrenergic agonists generally lower IOP, these agents can also cause an initial transient rise in IOP in laboratory animals (90, 133, 141, 153, 195) and in man (103, 140, 149) when applied topically. Depending on the type and dose of agonist, the hypertensive effect can be observed with the initial administration (acute), which is the usual case with adrenergic agonists having strong α-adrenoceptor activity, or it may be manifested only upon repeated exposure on consecutive days (chronic), which is the usual case with relatively selective β_2-adrenoceptor agonists. In the acute phase, the hypertensive response to drugs with strong α-agonism was relatively brief, lasting approximately 45 to 60 minutes (141). Several experimenters (92, 141) have suggested that the delay in onset of the ocular hypotensive effect of an acute dose of epinephrine is due to a hypertensive phase that temporarily negates the increased outflow and/or decreased aqueous inflow. The acute ocular hypertension produced by these agonists has been attributed to: 1) the generation of prostaglandins (195); 2) an increase in intra- and episcleral venous pressure (99, 203); and (3) enhancement in tone of extraocular muscles (70, 153).

Although pretreatment with indomethacin has been shown to inhibit the rise in IOP evoked by acute administration of norepinephrine (suggesting involvement of prostaglandins) (195, 196), it should be noted that indomethacin is also a calcium antagonist (132). It seems possible that inhibition of the role of calcium in excitation-contraction coupling by indomethacin could conceivably diminish the hypertensive action of norepinephrine. It is paradoxical that norepinephrine, epinephrine, and phenylephrine can inhibit the rise in IOP produced by topically administered arachidonic acid presumably by producing functional antagonism (30). This creates somewhat of a conundrum where the hypertensive action of norepinephrine is presumed to be mediated by prostaglandins and yet α-agonists can inhibit the rise in IOP produced by administration of the precursor of prostaglandins. Perhaps the measurement of prostaglandins in aqueous humor during the hypertensive phase of the action of norepinephrine can solve these puzzling circumstances.

Langham and Palewicz (99) have proposed that the biphasic pressure response to norepinephrine in rabbits is due in part to α-adrenoceptor effects on the outflow tract. It was hypothesized that increases in pressure and resistance to outflow caused by norepinephrine were due to vasoconstriction of aqueous and episcleral veins whereas the decrease of pressure and outflow resistance were the result of vasoconstriction of the blood supply to the intrascleral venous plexus. Presumably it was believed that there was reduced filling by blood in the intrascleral plexus resulting in more channels available to the outflow of aqueous humor. Both phases of the IOP response to norepinephrine could be antagonized by prior i.v. phenoxybenzamine, but the hypertensive phase was not inhibited by propranolol in this study. The initial, brief ocular hypertensive effect to single doses of isoproterenol or epinephrine has been reported to be antagonized by propranolol suggesting that it was a β-receptor-mediated response (91, 133). However, it was reported that this effect was also blocked by phenoxybenzamine, suggesting a primary α-receptor mediated action (196). It should be noted that phenoxybenzamine has ocular hypotensive actions of its own and that this complicates the interpretation of these results (97). Thymoxamine (2.5%) reduced the delay in onset of the hypotensive action of epinephrine, which suggested that the adrenoceptor mediating the delay is α in nature (92). It has been known for some time that the increase in tension of extraocular muscles caused by administration of sympathomimetic amines or by stimulation of the superior cervical ganglion can be antagonized by the α-adrenoceptor antagonists, phentolamine and phenoxybenzamine (37). It should be noted that propranolol has been reported to have a curare-like action on cholinergic receptors in rat extraocular muscles (24) in addition to its relatively strong local anesthetic activity.

Subsequently, it has been demonstrated that surgical transection of three major extraocular muscles in the rabbit abolished the acute hypertensive action of epinephrine (153) and that the sole response elicited was a

reduction in IOP. Other workers have also suggested that adrenergic agonists can contract extraocular muscles in the cat (37) and the rat (70). In the rat, the hypertensive effect of clonidine could be inhibited by antagonists of the cholinergic receptor at the neuromuscular junction (70), suggesting a possible indirect effect of clonidine on acetylcholine release and extraocular muscle contraction.

The mechanism of the ocular hypertensive response to β-adrenoceptor agonists in rabbits after chronic administration on consecutive days has not been elucidated but appears to be mediated by a change in responsiveness of β-adrenoceptors because the hypertension can be antagonized by prior administration of timolol (142). There is a temporal difference in the hypertensive response to acute as compared to chronic administration of adrenergic agonists. The ocular hypertensive response to a single (acute) dose of α-adrenoceptor stimulants (dopamine, norepinephrine, epinephrine, and phenylephrine) peaked much more rapidly (within one-half hr after administration) and was short-lived. In contrast, the response to consecutive (chronic) doses of β-adrenoceptor agonists (*l*-epinephrine, reproterol, and *l*-isoproterenol) tended to reach the peak more slowly (one to two hours after administration), was longer-lasting, and was usually much greater in terms of absolute change (about 6 to 10 mm Hg with consecutive daily application as compared to 2.5 to 4 mm Hg with a single application). Also of interest was the fact that the hypertensive response to consecutive (chronic) doses of β-adrenoceptor agonists occurred in normal eyes and in eyes in which the extraocular muscles had been transected whereas the acute (single-dose) hypertensive response to α-adrenoceptor agonists was suppressed markedly by surgical transection of extraocular muscles. These data reinforce the suggestion that the acute hypertensive response to certain adrenergic agonists is generated by contraction of extraocular muscles and is presumed to be an α-adrenoceptor-mediated event (153). On the other hand, the ocular hypertension resulting from repeated administration of other adrenergic agonists with α- and β-adrenoceptor activity probably is mediated by a β-adrenoceptor-related mechanism, possibly involving increased aqueous humor secretion (142).

In the treatment of glaucoma patients with a combination of guanethidine (3%) and epinephrine (0.5%), a biphasic response of IOP was observed (69). In two groups of patients it was demonstrated that during the rise in IOP (2.8 mm Hg increase) there was a 36% increase of aqueous humor production with a dilated pupil and an unchanged coefficient of outflow. Aqueous humor production was increased three hours after administration of the drugs. It was noted by these investigators that the IOP increase coincided with hyperemia of the conjunctiva and possibly with similar vasodilation of the vascular bed of the ciliary processes. Although the vasodilation was attributed to rebound vasodilation after α-stimulation, it seems reasonable to consider that the hyperemia and increased aqueous production could have been due to β_2-adrenoceptor stimulation.

VI. Species Differences in Adrenergic Innervation and Response to Adrenergic Drugs

There are species variations in the sympathetic innervation to the ciliary body, and the innervation of the chamber angle seems to vary between different species also. In subprimate species, the number of adrenergic terminals vary from very many in the guinea pig to very few in the rabbit, rat, and mouse (39). In rabbits, mice, rats, swine, and sheep, adrenergic fibers are seen scattered in the loose tissue of the trabecular region around Fontana's space (177). In dogs and cats, adrenergic fibers seem to be arranged radially in the tissue strands at the chamber angle. Although both types of autonomic neurons (adrenergic and cholinergic) have been found in the ciliary body in the monkey (101), only the stromal part of the ciliary process and possibly the basal surface of the pigmented epithelial cells appear to be innervated by the adrenergic system. Neuronal varicosities are found in the large vessels and in the stroma directly beneath the ciliary epithelium in various primates (38). In primates, adrenergic fibers are found only in the uveal portion of the trabecular tissue, running meridionally and radially. There is marked variation in adrenergic innervation of the trabecular meshwork within primate species (39); usually none in Cynomolgus monkeys and vervets, few fibers in owl and squirrel monkeys and moderate numbers of varicosities in Cebus monkeys and baboons. No adrenergic neurons have been around Schlemm's canal in primates, but neurons are present along the aqueous drainage veins. In the baboon, where density of innervation of the uveal trabecula is high, it seems that adrenergic nervous control of uveoscleral flow is a strong possibility.

Stimulation of sympathetic innervation to the eye produces different effects in different species. A slight rise followed by a fall in IOP was observed after stimulating the sympathetic nerves in dogs (102) and cats (37, 102). In the rabbit, adrenergic nerve stimulation increased outflow of aqueous humor slightly (54, 168) but did not cause a rise in IOP as it did in dogs and cats (62). However, in the vervet monkey stimulation of the cervical sympathetic trunk resulted in either no change or a decrease in outflow with a slight increase in inflow (11).

In considering species differences in response to drugs and nerve stimulation, it is important to note that there are differences in the anatomy of rabbit and primate eyes other than differences in sympathetic innervation. For example, the rabbit eye lacks a ciliary venous plexus, Schlemm's canal, trabeculae, aqueous veins, and efferent ciliary veins (119). Moreover, the ciliary muscle is less abundant in the rabbit than in the eye of primates. These observations suggest that differences in anatomical struc-

tures may result in qualitative and quantitative differences in response to adrenergic drugs and possibly to stimulation of sympathetic neurons.

The distribution of adrenoceptors in the ciliary muscle appears to differ between species according to the available pharmacodynamic evidence. In the cat and monkey, the receptors are reported to be predominantly β with some α and exclusively β with no α, respectively (119). In the rabbit, the predominant adrenoceptor in the ciliary muscle is reported to be mainly α with few β (4). Comparative data are needed for distribution of adrenoceptors in the ciliary epithelium and trabecular meshwork in various species including humans.

In terms of agonist activity, drugs with β_2-adrenoceptor stimulating activity seem to be most effective in lowering IOP in rabbits (141, 152). Agonists with greater selectivity for α_2-adrenoceptors, such as clonidine and α-methylnorepinephrine, are very effective ocular hypotensive agents in all species. In contrast, agonists with predominantly α_1- or β_1-adrenoceptor-stimulating properties are relatively weak ocular hypotensive agents in most species tested.

In vervet monkeys, injection of isoproterenol into the anterior chamber caused an increase in outflow facility (129), but α-adrenoceptor stimulation produced no increase in outflow facility (13). However, Green and Padgett (57) have demonstrated that norepinephrine, a strong α-agonist with β_1-adrenoceptor-stimulating properties, can increase true outflow facility in the rabbit. Therefore, it would appear that there are species differences in response to adrenoceptor stimulation in the outflow tract.

In the rabbit, stereospecificity does not seem to be important in lowering IOP in that *d*-isomers of some adrenergic agonists appear to be as active as *l*-isomers (75, 155, 173). However, in terms of hypertensive activity observed with chronic therapy of β-agonists in the rabbit, the β-adrenoceptor mediating the response showed specificity for the *l*-isomer (142), that is, *l*-isoproterenol elicited a hypertensive response but the *d*-isomer did not. In contrast, β-adrenoceptors mediating ocular hypotension in the eyes of monkeys and humans seem to be activated only by levorotatory isomers of adrenergic agonists (75).

In the case of β-adrenoceptor antagonists, experiments utilizing experimental animals have suggested that timolol is much less active in rabbit (131) and cat (27, 113) eyes than it is in human eyes (76, 207). This seems to be true for other nonselective and relatively selective β-adrenoceptor antagonists as well. Neufeld (131) reported that in rabbits the moderate ocular hypotensive effect of timolol was of longer duration than its association with β-adrenoceptors. These data suggested that timolol may lower IOP in rabbits in part by some mechanism other than β-adrenoceptor antagonism. Timolol has been reported to be ineffective (152) or only moderately effective (192) in preventing the ocular hypertension in rabbits caused by water loading and α-chymotrypsin treatment. Macri et al. (113) reported that timolol did not lower IOP, did not decrease aqueous humor formation nor did it inhibit isoproterenol-induced decrease in aqueous humor formation in the perfused cat eye, but in vivo studies in cats have shown ocular hypotensive activity (27, 107). This apparent discrepancy may reflect the need for ongoing sympathetic tone (which is lacking in the perfused cat eye) in order to observe the effects of timolol.

VII. Effects of Adrenergic Drugs in Experimentally Induced Ocular Hypertension

Animals models of glaucoma (or in certain cases more accurately ocular hypertension) permit extensive and invasive investigations of drug actions under circumstances that are not permissible in humans (see table 1). The species most frequently used in these studies are rabbits, dogs, chickens, and subhuman primates (50). The general disadvantage of most animal models, with the exception of subhuman primates, is that the iridocorneal angle anatomy is topographically different from that of the human. Although all species seem to have a continuous endothelial lining of the aqueous outflow channels, there are major differences in the pectinate ligaments, density of ciliary body musculature, scleral venous plexus (instead of Schlemm's canal), and extent of adrenergic innervation.

A. Methods of Inducing Ocular Hypertension (or Glaucoma) Experimentally

The water-loading procedure has been used clinically for many years as a provocative test in assisting the diagnosis of primary open-angle glaucoma (105). In experimental studies, the water load can be administered by the i.v. route or by orogastric intubation. The water

TABLE 1

Experimental models of ocular hypertension (or glaucoma) used for pharmacological evaluation

Method	References
Acute induction of inflammation (chemical burns, blunt trauma of the globe, aqueous chamber paracentesis, application of arachadonic acid)	30, 44, 53
Acute increased inflow of fluid by induction of a hypo-osmolar state (orgogastric water loading, i.v. injection of 5% glucose)	17, 172
Chronic blockage of aqueous outflow (injection of red blood cell ghosts, ligation of blood vessels posterior to globe, cautery of subconjunctival vessels, intracameral injection of α-chymotrypsin, circumferential laser photocoagulation of the trabecular meshwork)	48, 144, 167
Induction by constant exposure to light in chicken or light-dark cycling in rabbit	80, 156
Chronic drug administration (corticosteroids, β-adrenergic agonists)	18, 142
Acute age-related ocular hypertension (monkeys)	34
Chronic spontaneous (genetic) glaucoma (rabbits, dogs)	45, 51, 84

loading method produces a transient elevation in IOP and may be repeated at appropriate intervals to test the duration of the drug effect (172). It is believed that the reduction in blood osmolality results in water transfer into the eye sufficient to increase IOP (49). Others have suggested that the rise in IOP evoked by water loading in rabbits may be due to a decrease in outflow facility caused by hydrating the cells of the trabecular meshwork (185).

Another method for elevating IOP on a more chronic basis involves the injection of α-chymotrypsin directly into the eye. It was observed that after α-chymotrypsin was injected into the eyes of patients undergoing cataract surgery there was a transient rise in IOP accompanied by a decrease in outflow facility (81). This technique has been used successfully in owl monkeys (60) and rabbits (167).

A third experimental model involves the development of buphthalmia (hydrophthalmus, congenital infantile glaucoma) in rabbits having an autosomal recessive gene (bu) for this trait (45). These animals have an inability to maintain normal fluid relationships within the eye and develop labile ocular hypertension.

A fourth model utilizes the injection of glutaraldehyde-fixed ghosts of red blood cells (RBC) into the chamber of rabbits and monkeys (144). The cellular debris in the α-chymotrypsin and RBC ghosts models is presumed to block outflow of fluid through the trabecular meshwork. This type of sustained elevation of IOP in the latter model can occur clinically in eyes that harbor ghost red cells, for example, after severe intraocular hemorrhage.

A fifth model of glaucoma involves repeated, circumferential photocoagulation of the trabecular meshwork area in the anterior chamber angle of the eyes of rhesus monkeys (48). This technique caused a sustained elevation of IOP, reduction of outflow facility, and retinal and optic nerve changes similar to those seen in human chronic, open-angle glaucoma. Since the outflow tract is irreversibly damaged by this procedure, it would be most suitable for investigating drug effects on aqueous humor production; that is, it would be less appropriate for examining the action of drugs on outflow.

B. Some Examples of Antihypertensive Efficacy of Adrenergic Drugs

Experimentally, epinephrine not only lowered IOP in normal eyes of rabbits, but it also lowered IOP that was elevated by injection of α-chymotrypsin (127), by ocular instillation of formalin (44), by orogastric waterloading (152, 172), by topical administration of arachidonic acid (30), and by genetic predisposition in the glaucomatous eyes of beagles (51). Similarly, norepinephrine, epinephrine, and phenylephrine were effective in inhibiting the rise in IOP elicited by arachidonic acid in rabbits (30).

β-Adrenoceptor agonists with strong action on β_2-adrenoceptors seem to be most effective in suppressing the rise in IOP caused by water loading (152). Isoproterenol produced a prolonged, bilateral inhibition of water-induced ocular hypertension in rabbits. Two relatively selective β_2 agonists, terbutaline and reproterol, were also effective antihypertensive agents, but their effects were unilateral. The relatively selective β_1 agonists, tazolol and dobutamine, were minimally effective in this model of ocular hypertension. Drugs that were relatively inactive in this model included the mixed (α and β) agonist ephedrine and the β-adrenoceptor antagonists, timolol, propranolol, butoxamine, and metoprolol. From this study, it was concluded that this model would be a poor experimental method for screening in the IOP-lowering activity of β-adrenoceptor antagonists. However, in more recent studies it was shown that prazosin, a relatively selective α_1-receptor antagonist (124, 154), and labetalol, a drug capable of antagonizing α- and β-adrenoceptors (123), effectively suppressed the increase in IOP elicited by i.v. or oral water loading. Propranolol and clonidine proved to be moderately effective in lowering IOP in corticosteroid-induced ocular hypertension in the rabbit (18).

Limited evidence suggests that adrenergic agonists, especially those that stimulate the β-adrenoceptors, were most effective in lowering IOP in the animal models alluded to previously. β-Adrenoceptor antagonists generally showed very little or no activity in water-loaded rabbits; however, Vareilles et al. (192) reported that 0.5% timolol caused a large decrease in IOP in rabbits with experimental ocular hypertension due to α-chymotrypsin pretreatment. At this time, a versatile and suitable animal model for effectively screening adrenergic drugs with potential for use in treating human ocular hypertension or primary open-angle glaucoma has yet to be developed.

VIII. Summary, Conclusions, and Speculations

Pharmacological manipulation of the adrenergic system in the eye can produce favorable influences on aqueous humor dynamics in eyes afflicted with ocular hypertension and open-angle glaucoma. Adrenergic drugs can act at vascular and epithelial sites in the ciliary process to alter ultrafiltration and secretion of aqueous humor, respectively. Both α- and β-adrenoceptors are presumed to be present in the afferent and efferent blood vessels to the ciliary processes, and it is likely that both types of adrenoceptors can affect the rate of ultrafiltration. The predominant subpopulation of adrenoceptors in the ciliary epithelium of the rabbit, as shown by receptor binding studies, is β_2. Based upon this and other evidence, it can be postulated that secretion of aqueous humor can be modulated in most species by stimulation or inhibition of the β-adrenoceptor in the ciliary process. Thus, an adrenergic drug with mixed agonist activity, such as epinephrine, has the capacity to diminish formation by altering ultrafiltration (α) through vasoconstriction but, under certain circumstances, can increase formation by stimulating secretion (β). Antagonist drugs, such as timolol, can be conceived to diminish aqueous

humor formation either by augmenting α-adrenoceptor-induced tone to the afferent vessels of the ciliary processes, thereby decreasing ultrafiltration, or by depressing β-adrenoceptors competitively in the nonpigmented cells of the ciliary epithelium, thereby suppressing secretion (the latter process playing a greater role in total aqueous formation than the former).

In the aqueous outflow system, adrenergic drugs may act at the endothelial cells lining the trabecular meshwork and/or Schlemm's canal, on the vessels of the intrascleral plexus where blood and aqueous humor compete for outflow channels, and/or the episcleral veins that collect both blood and aqueous humor. Adrenergic agonists may also modulate the production of glycosaminoglycans in the outflow tract. Both α- and β-adrenoceptors are believed to function in the outflow tract of the rabbit, but β-adrenoceptors are proposed to predominate in the trabecular meshwork of primates.

Based upon experimental findings, conjecture is in order regarding the role of α- and β-adrenoceptors in regulating IOP. One might speculate, as others have, that alterations in sympathoadrenal function, such as alterations in the number and/or reactivity of peripheral and/or central pre- and postsynaptic adrenoceptors can lead to the pathophysiological changes resulting in ocular hypertension or glaucoma. With advancing age, alterations in density of innervation and receptor population may also be contributory to functional modifications that predispose to glaucoma.

In all likelihood, adrenergic drugs can lower IOP by acting at both peripheral (intraocular) and central (extraocular) sites; moreover, this action can be mediated by both pre- and postjunctional (synaptic) adrenoceptors. The predominant α-adrenoceptor responsible for lowering IOP would appear to have characteristics of an α_2-type. This hypothesis is based primarily on data taken from rabbits where those agonists having greater specificity for α_2-adrenoceptors (α-methylnorepinephrine, clonidine) lowered IOP more effectively than agonists (phenylephrine) with greater α_1 selectivity. One might also speculate that β-adrenoceptors involved in outflow of aqueous humor (in the trabecular meshwork and outflow vessels) are more characteristic of the β_1 type whereas β-adrenoceptors involved in inflow of aqueous (in the vessels of the ciliary processes and in the ciliary epithelium) are more similar to β_2. This line of speculation regarding aqueous humor efflux is based upon the fact that epinephrine and isoproterenol can increase outflow rather effectively, but relatively selective β_2-agents, terbutaline and salbutamol, are virtually inactive. Adrenoceptor binding studies, activation of adenylyl cyclase, and pharmacological data support the important modulatory role of β_2-adrenoceptors in aqueous humor formation, particularly the secretory component. For example, stimulation of β-adrenoceptors can increase aqueous humor production in some species. Therefore, the assumption has been made that antagonism of existing β-adrenoceptor "tone" can result in a decrease in aqueous humor formation. Alternatively, one might surmise that inhibition of vascular β_2-adrenoceptors would augment vasoconstriction by α-adrenoceptor stimulation resulting in decreased blood flow to the ciliary process and diminished aqueous humor formation by the ciliary processes. Thus, inhibition of intraocular β-adrenoceptors provides at least two potential mechanisms by which β-antagonists such as timolol can suppress aqueous humor formation.

There are numerous new areas for research in adrenergic pharmacology of aqueous humor dynamics. Since most β-agonists are subject to uptake-2, that is, uptake followed by metabolism, it would be interesting to determine the effects of uptake-2 inhibitors on the activity of an agonist, such as isoproterenol. Although topically applied adrenergic drugs are presumed to produce their major effect locally on adrenoceptors in the eye, it seems worthwhile to consider neuroendocrine involvement in the action of adrenergic drugs. Indirect humoral mechanisms could involve, for example, vasopressin or the renin-angiotensin system. There is some evidence that neuroendocrine mechanisms play a modulatory role in the circadian variation of IOP. Since the swings in IOP are more pronounced in glaucoma, it would seem valuable to determine whether adrenergic manipulation of neuroendocrine function will dampen these oscillations. Denervation supersensitivity seems not only to elicit a greater hypotensive response to epinephrine, but on a chronic basis a biphasic response can occur. It would seem that much could be learned from denervation experiments with regard to neuroendocrine modulation of postjunctional receptor populations.

In conclusion, the adrenergic system represents an important mechanism for regulating aqueous humor dynamics. Although α- and β-adrenoceptors are found in the inflow and outflow tracts in the eyes of different species, there is minimal understanding of their relative types, numbers, and functions. Considerable work with relatively selective adrenergic drugs must be performed before a pharmacological profile of adrenergic modulation can be defined in the eye and the function of adrenoceptors in aqueous humor dynamics in various species can be elucidated.

Acknowledgments. The author's studies referenced in this paper were supported in part by the National Eye Institute (EY02156 and EY05403). The author also wishes to acknowledge thankfully the contributions of his fellow scientist, J. M. Rowland, and the competent secretarial assistance of Betty R. Brashears.

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