Vasoactive agents on this preparation may have important implications for these substances in controlling ocular blood flow.

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Key words: norepinephrine, serotonin, histamine, a research support grant from the University of Nebraska Medical Center. Submitted for publication Jan. 8, 1974.

Key words: norepinephrine, serotonin, histamine, dose-response curves, isoproterenol, ciliary artery, potassium, ocular blood flow.

REFERENCES


A pharmacodynamic study of the inhibitory effects of L-norepinephrine, L-epinephrine, and d, L-isoproterenol on aqueous humor formation in the enucleated, arterially perfused cat eye. Frank J. Macri and Stanley J. Cevario.

L-norepinephrine, L-epinephrine, and d, L-isoproterenol have been found to decrease the elevated aqueous humor formation induced by acetylcholine plus eserine (Ach+Es) in the enucleated, arterially perfused cat eye. Utilizing pharmacological criteria, their action was determined to be stimulatory on the E-1 sites of sympathetic, ganglion-like receptors. It has been reported that the Ach+Es-induced increase of aqueous humor formation is due to an increase of ultrafiltration probably brought about by constriction of efferent blood vessels from the ciliary processes. It is suggested here that the decrease in inflow brought about by the adrenergic amines is probably the result of vasoconstriction of efferent ciliary process blood vessels with a resultant decrease of ultrafiltration.

The use of an enucleated, arterially perfused cat eye for the study of aqueous humor dynamics has recently been published. The advantages of this preparation over in vivo experimentation are that influences of anesthetic agents, in all of their ramifications, can no longer influence the intraocular pressure. Centrally mediated reflexes, if they exist, are also nullified. Most importantly, the responses obtained on the eye by drug action no longer need be qualified due to possible systemic actions of absorbed drug.
ing the Kmit min⁻¹ of the I¹ albumin by a
cameral administration of I¹ tagged human serum
albumin, using a gamma probe. Calculations of
aqueous humor formation were made by multiply-
ing the Kₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑеле₁ ele₂ ele₃ ele₄ ele₅ ele₆ ele₇ ele₈ ele₉ ele₁₀ ele₁₁ ele₁₂ ele₁₃ ele₁₄ ele₁₅ ele₁₆ ele₁₇ ele₁₈ ele₁₉ ele₂₀ ele₂₁ ele₂₂ ele₂₃ ele₂₄ ele₂₅ ele₂₆ ele₂₇ ele₂₈ ele₂₉ ele₃₀ ele₃₁ ele₃₂ ele₃₃ ele₃₄ ele₃₅ ele₃₆ ele₃₇ ele₃₈ ele₃₉ ele₄₀ ele₄₁ ele₄₂ ele₄₃ ele₄₄ The subject of this report are the effects of some sympathomimetic amines on aqueous humor turnover and intraocular pressure in this isolated eye preparation, and an examination of their mechanism of action.

Methods. The procedure for the isolation and arterial perfusion of the cat eye has been reported. In brief, the eye is perfused through the ophthalmic artery at constant pressure utilizing Eagles Basal Medium. The temperature is maintained at 37°C and the pH at 7.3.

The rate of aqueous humor turnover was determined by following the rate of decay of intraocular pressure in the anterior chamber fluid. Using indirect methods, Eakins' reports that epinephrine applied to the cornea of humans decreased the rate of fluorescein turnover in the anterior chamber fluid. Using indirect methods, Eakins' reports that epinephrine applied to the cornea of humans decreased the rate of fluorescein turnover in the anterior chamber fluid.

The data in these experiments regarding "C" should be viewed with reservation since episcleral venous pressure was not measured.

The ability of adrenergic amines to decrease the rate of aqueous humor formation was first reported by Goldmann who found that epinephrine applied to the cornea of humans decreased the rate of fluorescein turnover in the anterior chamber fluid. Using indirect methods, Eakins' reports that epinephrine applied to the cornea of humans decreased the rate of fluorescein turnover in the anterior chamber fluid.

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found, in rabbits, that intravitreally applied epinephrine and isoproterenol reduced the rate of aqueous humor formation while norepinephrine was essentially inactive. Kupfer, Gaasterland, and Ross7 and Gaasterland and co-workers8 found in humans that topically applied epinephrine and isoproterenol decreased the rate of aqueous humor formation while norepinephrine increased it.

It has been reported that the administration of acetylcholine plus eserine produces marked increases in the rate of aqueous humor formation of IOP and of “C.” The mechanism for this action was ascribed to stimulatory effects on E-2 sites of local sympathetic ganglion-like receptors. These Ach+Es-induced ocular responses have been reproduced in the current experiments. In the experiments reported here, the intra-arterial administration of l-epinephrine, l-norepinephrine, and d, l-isoproterenol had no effect on the untreated eye, but were active in reducing the elevated aqueous humor production, IOP, and “C” induced by the administration of Ach+Es. The inhibitory actions of the three adrenergic amines were effectively blocked by C-6, but only when the C-6 was administered before the Ach+Es. C-6 is a ganglionic blocking agent whose action is on E-2 sites of ganglionic receptors. It would appear, therefore, that the inhibitory actions of l-norepinephrine, l-epinephrine, and d, l-isoproterenol must be brought about by an agonistic action on these E-1 sites of ganglion-like receptors. C-6 has not been demonstrated to have any activity on α- or β-adrenergic receptors.

The three adrenergic amines have been shown to produce a vasoconstriction in the isolated, arterially perfused iris-ciliary body preparation. The mechanism for the vascular constriction by these agents, in the cases of l-epinephrine and d, l-isoproterenol, was concluded to be due to stimulation of E-1 sites on sympathetic ganglion-like receptors. This report also concluded that the action of norepinephrine was primarily on α-adrenergic receptors. In this latter instance, it is possible that l-norepinephrine also stimulated E-1 receptor sites but that the effect was masked by the much greater activation of α-receptors.

The data presented in this report regarding the sites of action of the three studied adrenergic amines on aqueous humor dynamics are compatible with the above-noted mechanisms on the vascularature of the anterior segment of the eye. Further evidence that the three amines are capable of stimulating E-1 sites has been recently reported for the salivary gland of the rat.11

It has been reported that the increase in aqueous humor formation induced by Ach+Es is due to an increase in ultrafiltration as a consequence of vasoconstriction of efferent blood vessels of the ciliary processes. Since the adrenergic amines are also vasoconstrictors and were effective in reducing the aqueous humor flow brought about by this mechanism of action, we are tempted to suggest that the adrenergic amines reduce aqueous humor flow by a mechanism involving vasoconstriction of afferent blood vessels to the ciliary processes. This vasoconstriction would reduce intravascular pressure and consequently reduce ultrafiltration.


REFERENCES


Table 1. D, L-isoproterenol (6)

<table>
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<th></th>
<th>I</th>
<th>IOP</th>
<th>&quot;C&quot;</th>
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<td>±0.75</td>
<td>0.62</td>
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<td>10.29 (NS)</td>
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<td>±4.76</td>
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Efferent limb protection of corneal allografts from immune rejection. STEPHEN R. WALTMAN AND JOEL M. ENGELSTEIN.

Twenty-six rabbits with clear 6.5 mm. penetrating corneal allografts had skin grafts from the same donor eight weeks later. Ten animals rejected their corneas within 16 days. Two and one-half weeks after skin grafting eight of the remaining 16 rabbits had 5.5 mm. corneal buttons excised and resutured within the first graft. These grafts were all rejected 23 to 26 days after skin grafting. Of the eight grafts which were not excised, four remained clear and four were rejected 27 to 30 days after skin grafting. Without intervening skin grafts, all 10 re-excised corneal allografts remained clear. These results indicate that when afferent immune protection is short-circuited by sensitization with skin grafts some corneal grafts are protected from the afferent immune arc by corneal anatomy. When this anatomy is interrupted, efferent protection is abrogated, resulting in an increased graft rejection rate and decreased graft survival.

In rabbits1, 2 and man,3 nonrejected penetrating corneal allografts (PKP's) do not sensitize the host. Therefore, a major factor protecting PKP's from immune rejection is a block in the afferent limb of the immune arc. In the present study, subsequent skin grafts from the same donor animals were used to sensitize the host and eliminate this afferent limb protection. We then studied the efferent limb of the immune arc in well-healed corneal transplants.

Materials and methods. Six and one-half millimeter penetrating corneal allografts were exchanged between pairs of virgin New Zealand white rabbits weighing 2.5 to 3.5 kilograms. The members of each pair were from two partially inbred strains.4 Continuous 8-0 silk suture was used, and topical antibiotics and dilating drops were applied daily until suture removal on Day 10.