AMP, the 8-methylthio derivative, perfused into observation supports the hypothesis that cyclic-AMP mediates the action of adrenergic agents to this fluid into venous channels, predominantly via the anterior chamber of the eye of the vervet state level by the continuous production of aqueous ops), the trabecular meshwork and canal of Schlemm. The flow of aqueous humor out of the nonhuman primate eye can be influenced by adrenergic agents, that in the rabbit exert part of their action via adenosine 3',5'-monophosphate (cyclic-AMP). We have measured the outflow facility of the primate eye. In this investigation, an analogue of cyclic-AMP increases the outflow facility of the eye of the vervet monkey and report evidence that cyclic-AMP mediates the action of adrenergic agents to reduce intraocular pressure in the primates.

Intraocular pressure is maintained at a steady-state level by the continuous production of aqueous humor by the ciliary processes and drainage of this fluid into venous channels, predominantly via the trabecular meshwork and canal of Schlemm. The flow of aqueous humor out of the nonhuman primate eye can be influenced by adrenergic agents, that in the rabbit exert part of their action via adenosine 3',5'-monophosphate (cyclic-AMP). We have measured the outflow facility of the eye of the vervet monkey and report evidence that cyclic-AMP mediates the adrenergic action to increase the outflow of aqueous humor from the primate eye.

Methods. Vervet monkeys (Cercopithecus ethiops), weighing 4 to 7 kilograms, were anesthetized with phencyclidine and sodium pentobarbital and each anterior chamber was prepared with three cannulas. In each eye, outflow facility was measured through one cannula, as previously described, by perfusion at two levels of constant pressure, usually 2.5 and 12.5 mm Hg above the prevailing intraocular pressure, approximately 9 mm Hg. To deliver an artificial aqueous humor solution into the anterior chamber, without changing intraocular pressure, two cannulas were connected to two identical syringes, coupled to push and pull the solution simultaneously. The artificial

<p>| Table I. Effect of 8-methylthio cyclic-AMP on outflow facility in the vervet monkey |
|----------------------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outflow facility (uI/min/mm. Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.26 ± 0.02 (10)</td>
<td>0.34 ± 0.04 (10)</td>
</tr>
<tr>
<td>8-methylthio cyclic AMP</td>
<td>0.28 ± 0.03 (6)</td>
<td>0.61 ± 0.06 (6)</td>
</tr>
</tbody>
</table>

*Mean ± S.E.M. (number of eyes).

tion of the one described by Bárany as follows: 140 mM NaCl, 5 mM KCl, 1 mM CaCl₂, 0.3 mM Na₂HPO₄, 5.5 mM glucose, and 1 mM ascorbic acid at pH 7.4.

Results. Table I shows the results of these experiments. In the control eye, after approximately 12 ml of artificial aqueous humor were delivered over a period of about 30 minutes, some increase in outflow facility occurred, probably due to an increase in tone of the ciliary muscle. In the opposite eye of the same animal, perfused with artificial aqueous humor containing 5 mM 8-methylthio cyclic-AMP (SQ 80,002), outflow facility doubled within 45 minutes of the start of the perfusion. This increase in outflow facility lasted at least one hour and in one animal was observed for six hours. Pupillary diameter was unaffected.

Discussion. The value for outflow facility before treatment of the eye of the vervet monkey that we have obtained is less than the value obtained by Bárany and Bill, but more closely approximates the value in rabbits and man. The difference might be explained by longer anesthesia time and decreased tone of the ciliary muscle during our experiments. We have replicated, satisfactorily, other influences on outflow facility in these monkeys. Thus, intramuscular hexamethonium decreased outflow facility, intracameral injection of pilocarpine increased outflow facility several fold, and intracameral perfusion of isoproterenol increased outflow facility approximately 50 per cent.

We have hypothesized that elevated levels of cyclic-AMP, in tissues that govern outflow resistance, lead to an increase in the rate of outflow of aqueous humor. In support of this hypothesis, we previously demonstrated that elevating local cyclic-AMP levels in the outflow channels of the rabbit eye by a single injection of 5 µl of 10⁻² M cyclic-AMP into the anterior chamber, leads to a decrease in intraocular pressure and an increase in outflow facility. Several preliminary experiments with the vervet monkey indicated that a single injection of 5 µl of 10⁻² M cyclic-AMP or its analogues into the anterior chamber does not influence outflow facility.
cyclic-AMP: by "push-pull" perfusion of the anterior chamber. We found that the 8-methylthio derivative of cyclic-AMP produces a twofold increase in outflow facility, similar to the results obtained with isoproterenol, perfused in the same manner.2

With intracocular delivery, in rabbits, both alpha- and beta-adrenergic compounds increase the outflow of aqueous humor, while, in monkeys only compounds with beta-adrenergic activity are effective.2 We conclude that adrenergic agonists, that can stimulate the synthesis of cyclic-AMP, increase the outflow facility of the eye by a mechanism mediated by this cyclic nucleotide. In man, where the pharmacological mechanisms are not clear, topical epinephrine increases outflow facility when used successfully in the treatment of primary open-angle glaucoma.10 Therefore, increasing the rate of synthesis of cyclic-AMP may be important to the medical management of glaucoma. Further investigations into compounds that stimulate or potentiate the cyclic-AMP system may provide additional approaches to the treatment of this disease.

We gratefully acknowledge the expert technical assistance of Barbara Brown, Sidney M. Hess, Ph.D., of the Squibb Institute for Medical Research kindly provided the gift of SQ 80,002.

From the Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, Conn. 06510. This work was supported in part by United States Public Health Service Grants EY 00943, EY 01470, EY 00237, and EY 00485. Submitted for publication April 23, 1975.

Key words: cyclic-AMP, outflow facility, aqueous humor, intraocular pressure, primate, catecholamines, glaucoma.

REFERENCES


The peak velocity-amplitude characteristics of voluntary saccades and the fast phases of caloric, rotational, and optokinetic (OKN) nystagmus were compared in ten human subjects in both light and, except for OKN, darkness. All these fast eye movements had similar velocities and all slowed in darkness. This study supports the presumption that the identical brainstem firing patterns found in monkeys for all fast eye movements also occur in man.

Fast eye movements (FEM) include voluntary and reflex saccades and the fast phases of nystagmus.1 In monkey, all types of FEM are produced by identical nuclear2 and prenuclear3 burst patterns. There is substantial evidence in both humans4 and monkeys5 that the pontine paramedian reticular formation at the level of the abducens nuclei is the final prenuclear generator for all FEM. Although many studies have defined the velocity-amplitude characteristics of voluntary reposition saccades, there is a paucity of information concerning intrasubject comparisons of these saccades with nystagmus fast phases. We are reporting such a study of voluntary saccades and nystagmus fast phases induced by caloric, rotation, and optokinetic (OKN) stimuli performed in illuminated laboratory conditions and, except for OKN, in darkness.

Methods. Ten normal volunteers, aged 25 to 40 (six women and four men), served as subjects. None had used sedatives, hypnotics, stimulants, or anticonvulsants within a week preceding the study. Eye movements were recorded by an infrared reflection device mounted on spectacle frames. Eye position signals were DC coupled to a pen-writing