

THE MECHANISM OF ACTION OF CERTAIN ORGANOPHOSPHORUS MIOTICS

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The object of this investigation was to determine whether organophosphorus compounds used in the treatment of glaucoma — phosarbin (tetraethyl monothiopyrophosphate), armin (ethyl-p-nitrophenyl ester of ethylphosphinic acid), nibufin, and preparation No. 11 — have a direct action on the sphincter of the iris.

EXPERIMENTAL METHOD

Experiments were conducted on cats and rabbits from which the ciliary ganglion had been removed. The total number of animals undergoing operation was 28. In the cats the operation was performed under ether anesthesia, and in the rabbits under chloral hydrate (10 ml of a 7% solution/kg body weight). Besides the above procedure, some cats and rabbits received a retrobulbar injection of 1.5 ml of 1% novocain solution. A skin incision was made from the outer angle of the eye horizontally towards the concha auriculæ (5-6 cm long). The wound was extended along the superior and inferior borders of the orbit. By means of bone scissors and forceps the lateral wall of the orbit was removed. After an incision had been made in the orbital fascia the rectus lateralis muscle was seized with a blunt hook and divided from the sclera with scissors. The eyeball was fixed with a blunt hook and moved slightly anteriorly and medially. By following the course of the branch of the oculomotor nerve running to the rectus inferior muscle the ciliary ganglion was found, situated in the depth of the orbit, lateral to the optic nerve and orbital artery. It consists of a pink nodule, about 2 mm in diameter. The ganglion was seized with forceps and excised with scissors. The approach to the ciliary ganglion in the rabbit is complicated by the presence of the muscle drawing in the eye, and this had to be immobilized by blunt dissection. Occasionally in the rabbits very tiny accessory ganglia were found, and these were removed as far as possible.

The operation was performed on the right eye and the left eye served as a control. The criterion of complete removal of the ciliary ganglion and of degeneration of the postganglionic fibers of the oculomotor nerve was the following tests described by Leopold and Comroe [5]: dilation of the pupil on the operated side immediately after removal of the ciliary ganglion, absence of a reaction to light, immobility of the pupil on the operated side after instillation of 1% eserine solution, and an increase in sensitivity to 1% solutions of pilocarpine and carbachol by comparison with the control eye. The horizontal diameter of the pupil was measured with Haab's pupillometer.

EXPERIMENTAL RESULTS

Complete degeneration of the postganglionic fibers could be obtained in only 6 of the 18 rabbits undergoing operation. This was because of the presence of accessory ciliary ganglia in the rabbits, which were very difficult to find at operation. In 8 of the 10 cats undergoing operation the ganglionectomy was successful. Maximal dilation of the pupil, absence of a reaction to light, and an increase in the reaction to instillation of pilocarpine and carbachol by comparison with the control eye were observed in all 28 animals. A reaction to eserine, although very slight, was observed in 12 of the 18 rabbits and in 2 of the 10 cats.

To investigate the action of eserine, 2 drops of a 1% solution of the drug were instilled into the operated eye and 3 drops into the ganglionectomized eye. In all cases a general toxic action of eserine was found. This test is



Absence of reaction of the pupil to injection of phosarbin solution (3 drops, concentration 1:1000) one week after removal of the right ciliary ganglion.

left (control) eye. After total removal of the ciliary and accessory ganglia and subsequent degeneration of the postganglionic fibers we did not observe contraction of the pupil under the action of any of the investigated organophosphorus antiglaucoma compounds, even when used in 10 times the therapeutic concentration. Contraction of the sphincter under the action of the organophosphorus compounds could be detected only in cases when a reaction to 1% eserine solution was present. On the 2nd day after ganglionectomy contraction of the pupil was observed on the operated side under the action of phosarbin in a dilution of 1:10,000 but the pupil remained considerably larger than in the control eye. On the following days the degree of contraction diminished, and 7-8 days after the operation the pupil remained immobile even after instillation of 3 drops of phosarbin in a dilution of 1:1000 (see figure). At the same time the pupils of the ganglionectomized animals did not react to eserine. Our results are in agreement with the results of histological investigations showing that 6-7 days after removal of the ciliary ganglion typical Wallerian degeneration develops in the postganglionic fibers innervating the sphincter [1, 2]. Consequently, as degeneration of the neural elements takes place the sensitivity of the sphincter to organophosphorus compounds falls, and after degeneration administration of these compounds fails to cause contraction of the sphincter.

SUMMARY

Ganglionectomy of the ciliary ganglion in 6 rabbits and 8 cats produced the following effect: after degeneration of the postganglionic fibers the pupils failed to react to the instillation of 1% eserine and exhibited an increased sensitivity to 1% pilocarpine and 1% carbachol solutions. Phosarbin, nibufin, armin, and preparation No. 11 were tested on the eyes of these animals in therapeutic and 10 times therapeutic concentrations. The cholinesterase organophosphorus antiglaucoma preparations were found to have no direct effect on the iris sphincter.

LITERATURE CITED

1. V. N. Murat. *Trudy Kazansk. med. inst.* 1, v. 1, p. 7 (1948).
2. V. M. Tushnova. In book: *Morphology of the Autonomic Nervous System* [in Russian], p. 131. Moscow (1946).
3. V. M. Tushnova. In book: *Morphology of the Autonomic Nervous System* [in Russian], p. 135. Moscow (1946).
4. H. K. Anderson, *J. Physiol. (London)* (1905), v. 33, p. 414.
5. L. H. Leopold and J. H. Comroe, Jr., *Arch. Ophthalm.* (1946), v. 36, p. 17.

the most demonstrative, because immobility of the pupil to eserine in conjunction with positive results of the tests described above establishes the presence of complete degeneration of the postganglionic fibers of the sphincter. According to the available data [3, 4], constriction of the pupil after instillation of 1% eserine solution is evidence of incomplete denervation of the sphincter. In 6 rabbits and 8 cats the pupils remained immobile even after instillation of 3 drops of 1% eserine solution. In some animals the pupil of the ganglionectomized eye contracted by 1.0-1.5 mm and during the following days regeneration of the neural elements began, in the course of which the sensitivity to eserine and to organophosphorus compounds rose, while that to pilocarpine fell.

During the investigation of armin, phosarbin, nibufin, and preparation No. 11 tests were made of concentrations of the compounds used in clinical practice and of concentrations 10 times greater than therapeutic. Three drops were instilled into the right eye and 2 drops into the