PUPILLARY REACTIONS IN RABBITS EXPOSED TO SMALL DOSES OF Sr^{90}

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An important consequence of exposure of an animal to radioactive substances is a change in its reaction to drugs [2]. Despite its obvious current importance, insufficient attention has been paid to this problem.

In this communication we shall deal with the changes in the pupillary reactions, especially to pharmacological agents, after exposure of rabbits to strontium 90. Changes in the pupils during chronic exposure to ionizing radiation, and, more especially, the behavior of the pupillary reactions, are not discussed in the literature.

EXPERIMENTAL METHOD

Experiments were conducted on ten rabbits which received subcutaneous injections of strontium 90 in a dose of 5 μC/kg/day for a period of $2\frac{1}{2}$ months, and also on ten control rabbits. Most animals showed initial signs of chronic radiation sickness: a fall in the leucocyte count (to 4000-5000 per mm^3 blood) and an increase in the permeability of the skin vessels by 10-20% compared with the initial level, as shown by the results of the fluorescein test. In order to record the size of the pupils, a Zenith-S camera with intermediate rings Nos. 2, 3, and 4 and an objective set at 0.8 m was used (Fig. 1). The apparatus was mounted on a stand with the pentagonal prism below. A micrometer scale with divisions of 0.1 mm was inscribed directly on the opaque glass of the apparatus. The image of the eye was superimposed upon the scale on the opaque glass, and the experimenter was able to observe these with a magnification of five times, on account of the eyepiece of the apparatus. The size of the pupils (the lesser diameter) was measured directly during the experiment on the scale; the accuracy of measurement was verified after development of the film. The light source (a 75 w lamp) was placed at a distance of 30 cm from the rabbit's eye at an angle of 30° to the axis of its body. The intensity of illumination was verified by a photoelectric method.

In order to investigate the pupillary reactions, six pharmacological preparations were used, possessing different mechanisms of action on the pupils: a narcotic (morphine), ganglionic preparations (nicotine and tetraethylammonium) and also drugs acting mainly on the peripheral nerve endings (eserine, pilocarpine, homatropine). All these drugs were used in nontoxic doses, which caused no disturbances of the animals' general condition. With each drug from 6 to 10 experiments were carried out on control rabbits and animals treated with radiostrontium (the doses and methods of administration are given in the table). Experiments were performed at intervals of not less than three days.

EXPERIMENTAL RESULTS

On the basis of nearly 200 measurements of the size of the pupils, it was found that the pupillary diameter in the treated rabbits, when the eye was illuminated with 3000 lux, averaged 5.0 ± 0.1 mm (here and subsequently, the first number indicates the arithmetic mean, and the second the mean square deviation). In healthy animals, under the same conditions, the pupillary diameter was slightly smaller, namely, 4.6 ± 0.1 mm. With an illumination of 1000 lux, the size of the pupils in the treated and normal animals was the same, namely, 5.5 ± 0.1 mm. The reaction of the pupils to light was thus weakened in the experimental animals, although only slightly.

The results of the investigation of the pupillary reactions to the administration of pharmacological agents are shown in the table.

By way of illustration of the experiments, we give examples of the individual pupillary reactions in the

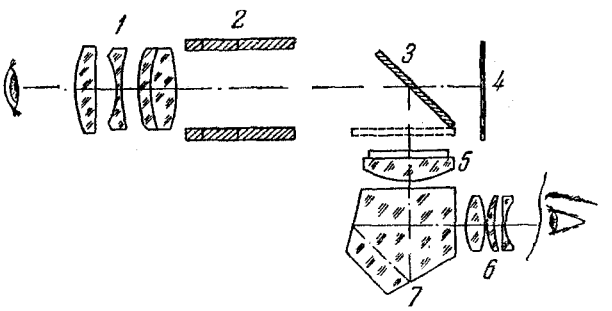

Fig. 1. Scheme of use of the Zenith-S camera for investigation of the pupillary reactions. 1) Objective; 2) intermediate rings; 3) mirror; 4) photographic film; 5) scale; 6) eyepiece; 7) pentagonal prism.

Pupillary Reactions in Rabbits Treated with Strontium 90 and in Controls

Drug	Dose and method of administration	Change in pupillary diameter (in mm)		Character of reaction
		experiment	control	
Morphine hydrochloride	0.2 ml/kg of 1% solution intravenously	1.0 ± 0.1	0.4 ± 0.1	Miosis
Nicotine	0.05 ml/kg of 0.1% solution intravenously	1.1 ± 0.2	0.4 ± 0.2	"
Tetraethylammonium iodide	0.25 ml/kg of 10% solution intravenously	2.5 ± 0.2	1.6 ± 0.1	Mydriasis
Eserine salicylate	2 drops of a 1% solution into conjunctival sac	3.0 ± 0.2	2.3 ± 0.2	Miosis
Pilocarpine hydrochloride	2 drops of a 1% solution into conjunctival sac	1.8 ± 0.1	1.7 ± 0.2	"
Homatropine hydrobromide	2 drops of a 1% solution into conjunctival sac	3.2 ± 0.3	3.2 ± 0.2	Mydriasis

experimental rabbits and compare them with the controls (Fig. 2).

Immediately after injection of morphine into the rabbits, we observed constriction of the pupils, and its intensity was 2.5 times greater in the experimental, than in the control animals. The miotic action of morphine is due to excitation of the oculomotor nerve center. This effect is most marked when morphine is given, by comparison with other narcotics [3]; it may possibly develop secondarily as the result of the action of morphine on the higher divisions of the brain, which control the center of the oculomotor nerves [1]. It is interesting that in our experiments, when fractional doses of narcotics (urethan and hexobarbital) were given, it was shown that the pupillary reaction to morphine was hardly affected by variation in the depth of narcosis; but in the last stage of narcosis, when profound depression and arrest of breathing and severe bradycardia were found, it was weakened and later produced no effect, showing depression of the medullary centers. The direct action of morphine on the oculomotor center cannot therefore be rejected. These experiments demonstrate the considerable increase in the sensitivity of this center to the action of morphine after exposure to strontium 90.

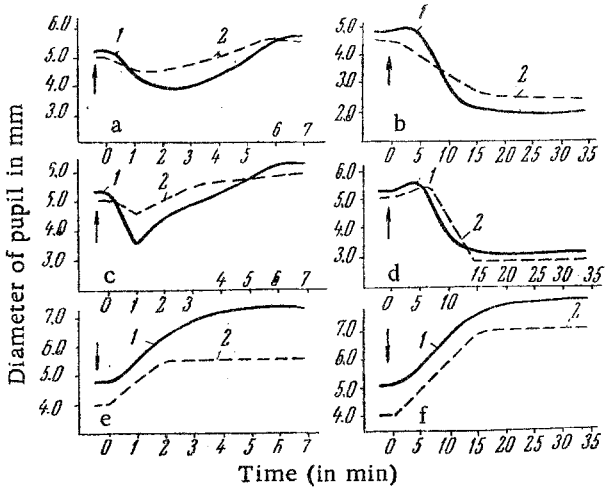

Fig. 2 Pupillary reactions to pharmacological agents in rabbits treated with strontium 90 (1) and in control rabbits (2). a) Morphine; b) eserine; c) nicotine; d) pilocarpine; e) tetraethylammonium; f) homatropine.

Injection of nicotine caused a transient constriction of the pupils, and the degree of miosis in the treated rabbits was almost three times greater than in the controls. Constriction of the pupils in response to nicotine is due mainly to its ganglionic action. Nicotine causes miosis by excitation of the nicotinelike cholinergic systems of the parasympathetic ganglia (in this case, the ciliary ganglion). We know from the literature that ganglion-blocking substances dilate the pupils. This property is fully shared by tetraethylammonium. As a result of the blocking of the parasympathetic and sympathetic (cervical) ganglia, dilatation of the pupils occurs as a result of the predominance of the dilator pupillae over the sphincter. In rabbits exposed to strontium 90, after administration of tetraethylammonium, the pupil was more strongly dilated than in the control animals. The results of these experiments indicate an increase in the sensitivity of the vegetative ganglia to the influence of ganglionic drugs.

Eserine, when instilled into the conjunctival sac, constricts the pupil because it is an anticholinesterase drug. As the table clearly shows, the miosis was rather more strongly expressed in the experimental rabbits than in the controls. In addition to its local action on the pupil, the resorptive influence of eserine must be borne in mind; it is revealed by the development of a profuse salivation. The miosis may therefore be dependent, not

only on the local action of eserine on the muscarine-like cholinergic receptors, but also on the nicotinelike cholinergic receptors of the ciliary ganglion. We found no significant difference between the miotic action of pilocarpine in the experimental and control rabbits. The same remark applies to the results of the experiments with homatropine, which causes mydriasis. The action of these two preparations is explained by their influence on the peripheral muscarinelike cholinergic systems. The sensitivity of these systems to pilocarpine and homatropine in the experimental rabbits was thus not changed. The more marked miotic action of eserine in the affected animals must evidently be attributed to an increase in the sensitivity of the nicotinelike cholinergic systems.

The increase in sensitivity to drugs with differences in their selective action cannot yet be given a detailed explanation. This fact is evidently caused by changes in different divisions of the nervous system (asthenization, alteration in the level of excitation, phasic conditions), and by disturbances of the enzyme and mediator (especially acetylcholine) metabolism. Increased permeability also leads to increased sensitivity to chemical substances [4]. The strengthening of the miotic action of drugs acting on the central nervous system and the vegetative ganglia may also be to some extent dependent on the weakening of the reaction to light in the experimental rabbits, for the initial diameter of the pupils when the experiments were carried out was slightly larger than that of the control animals.

The results obtained confirm the value of the pupillary reactions in the investigation of the functional state of an animal in chronic experiments.

SUMMARY

Experiments were conducted on rabbits with the initial signs of chronic radiation sickness. The following changes were observed in the affected animals: decrease of pupillary reaction to light and intensification of pupillary reactions induced by pharmacological substances affecting the central nervous system and the ganglionic apparatus (morphine, nicotine, tetraethylammonium). Reaction of the pupils to pilocarpine and homatropine remained unchanged.

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