EFFECT OF CHLORPROMAZINE ON DISTRIBUTION AND CONCENTRATION OF NUCLEIC ACIDS AND PROTEINS IN STRUCTURAL ELEMENTS OF THE RABBIT RETINA

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Intramuscular and, in particular, retrobulbar injection of chlorpromazine into rabbits lowers the concentration of RNA and proteins in certain elements of the retina. The greatest changes are observed in the bipolar cells and cells of the ganglionic layer. These changes are accompanied by lowering of ophthalmotonus and disturbance of visual function.

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To elucidate the mechanism of action of chlorpromazine on functions of the eye a histochemical study was made of the distribution of nucleic acids and proteins, substances closely connected with visual function [1, 2], in the retina.

EXPERIMENTAL METHOD

Experiments were carried out on 20 sexually mature rabbits subdivided into four groups: the animals of group 1 received chlorpromazine intramuscularly in a dose of 10 mg/kg daily for three days, the rabbits of group 2 received chlorpromazine in a dose of 20 mg/kg intramuscularly for three days, those of group 3 received 10 mg/kg intramuscularly for 30 days, and the rabbits of group 4 received 2 mg/kg chlorpromazine by retrobulbar injection daily for three days. Control animals received injections of physiological saline in a dose of 0.5 ml at the same times and by the same methods. The eyes of all animals were enucleated 6 h after the last injection.

In all experiments attention was directed toward the animals' behavior, the ophthalmotonus and, after retrobulbar injection of chlorpromazine, the state of the anterior portion of the eye.

Histological material was stained by Brachet's method for RNA, by Feulgen's method for DNA, and by the Danielli tetrazolium reaction for total protein.

EXPERIMENTAL RESULTS

After administration of chlorpromazine in a dose of 10 mg/kg for three days the animals became inactive and drowsy and their defensive and feeding reflexes were depressed. The intraocular pressure fell by 3-4 mm Hg in the course of 2-4 h. In the photoreceptors of the retina a decrease in concentration of RNA and amino acids was found in the inner segments of the rods and cones, while in the nucleocytoplasmic part of these cells the concentration of the substances investigated showed negligible changes. In the inner nuclear and ganglionic layers the number of cells showing signs of hypochromia was greater than in the control mainly on account of small and medium-sized bipolar and ganglionic cells with a lowered concentration of RNA and amino acids in their cytoplasm.

After administration of chlorpromazine in a dose of 20 mg/kg for three days, the animals were very drowsy for 4-5 h. Their intraocular pressure fell by 4-6 mm Hg, returning to its original level after 6-8 h. In the layer of photoreceptors of the retina, individual swollen cells and cells with granular degeneration

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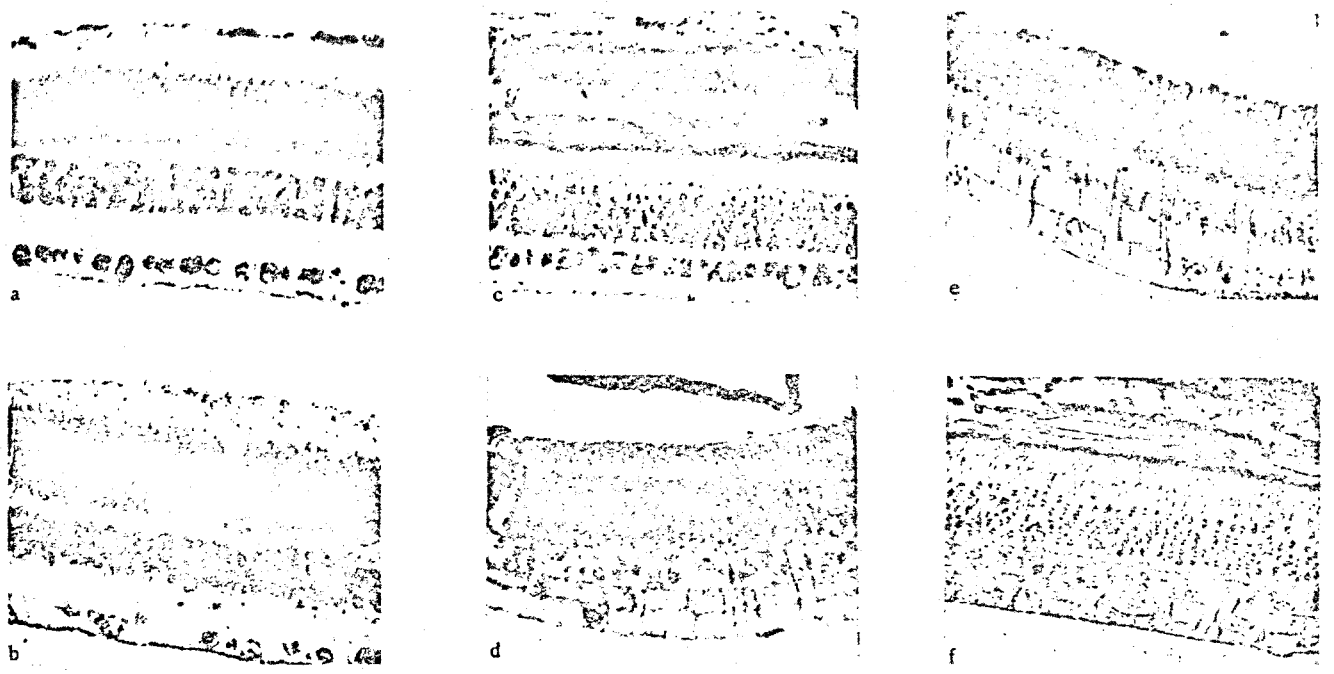

Fig. 1. Distribution of RNA (Brachet's method) and proteins (Danielli's tetrazolium reaction) in structural elements of the retina under normal conditions and after injection of chlorpromazine. a) Distribution of RNA in control animals; b) distribution of RNA after intramuscular injection of chlorpromazine in dose of 20 mg/kg for three days; c) distribution of RNA after retrobulbar injection of chlorpromazine in dose of 2 mg/kg for three days; d) distribution of proteins in control animals; e) distribution of proteins after intramuscular injection of chlorpromazine in dose of 20 mg/kg for three days; f) distribution of proteins after retrobulbar injection of chlorpromazine in dose 2 mg/kg for three days. Objective 20, ocular 10.

of the rods and cones were found. The concentration of RNA and amino acids in the rods and cones was lowered to a much greater degree (Fig. 1a, b, d, e) than after administration of chlorpromazine in a dose of 10 mg/kg. A decrease in concentration of RNA and amino acids was also observed in the nucleo-cytoplasmic region. The swollen cells were particularly deficient in RNA and amino acids, while the granular debris of the degenerated rods and cones gave a more intensive reaction for proteins.

In the inner nuclear and ganglionic layers vacuolation and swelling of the cells and their nuclei with evidence of chromatolysis were observed. Hyperchromic cells were absent. Compared with the controls, the medium-sized and small ganglionic cells showed considerable changes. Against a background of a general fall in concentration of RNA and protein in the nerve cells, a particularly marked decrease in their concentration was found in the hydropic cells. The concentration of RNA in the nucleolus and of amino acids in the karyoplasm and nucleolus was appreciably reduced, so that the nucleus became paler than usual. A decrease in intensity of the reaction for amino acids was also observed in the amorphous ground substance. The changes described were accompanied by absorption of yellowish-brown pigment by the retina and its neuronophagy by Mueller's cells.

After administration of chlorpromazine in a dose of 10 mg/kg daily for 30 days, during the last 10-15 days the general reaction and the state of ophthalmotonus were almost indistinguishable from those in animals receiving the drug in a dose of 20 mg/kg for three days. However, during long-term administration no signs of acute degeneration of the cells or of pigment absorption were found.

After three retrobulbar injections of chlorpromazine in a dose of 2 mg/kg the degree of drowsiness corresponded to the state of the animals after intramuscular injection of the drug in a dose of 20 mg/kg, but the fall of ophthalmotonus was much greater (by 5-10 mm Hg), and its initial level in some cases had not been regained even after 24 h. In the layer of photoreceptors, besides a decrease in concentration of RNA and amino acids (Fig. 1c, f) numerous cells with well marked chromatolysis and granular degeneration were found.

In the cells of the inner nuclear layer all stages of chromatolysis were detected—from perinuclear to complete—with corresponding reductions in the concentrations of RNA and amino acids.

In the ganglionic layer, besides cells showing signs of chromatolysis and with a lowered concentration of RNA, DNA, and amino acids, individual cells with evidence of plasmolysis and karyolysis were found. In cells with the latter changes the RNA concentration was lowered while the intensity of the reaction for amino acids and for their granular debris was increased. The concentration of RNA and amino acids in the Mueller's cells were considerably reduced. These changes were accompanied by more marked pigment absorption by the retina with neuronophagy of the pigment by Mueller's cells than after intramuscular injection of the maximal dose (20 mg/kg).

The morphohistochemical changes in the retina described above were observed mainly in small and medium-sized bipolar and ganglionic cells and to a lesser degree in the other cells, so that chlorpromazine may be said to have a selective action within the limits of a single structure.

A number of ophthalmologic investigations [4] have revealed changes in visual function under the influence of large doses of drugs of the phenothiazine series. As a result of electrophysiological investigation [3] a decrease in amplitude of the B wave on the electroretinogram was found, indicating changes in metabolic processes in the retina.

The results obtained suggest that one cause of the functional changes taking place in the retina under the influence of chlorpromazine is a disturbance of nucleoprotein and protein metabolism.

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