FUNCTIONAL AND MORPHOLOGICAL CHANGES IN THE SYSTEM OF THE HYPOTHALAMUS AND HYPOPHYSIS UNDER THE INFLUENCE OF THE NEUROTROPIC DRUG ETHYLNORANTIFEIN

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Ethylnorantifein is a member of a new class of neurotropic drugs synthesized in the Division of Pharmacology of the above institute [3]. The pharmacological analysis of these compounds, called antifeins, has demonstrated their high level of activity on the central nervous system and the variegated pattern of their activity on the individual structures and division of the brain [2, 5].

Experiments on different animals (rats, guinea pigs, dogs) have shown that the antifeins have a stimulant action on the glucocorticoid function of the adrenals and, if administered for long periods, prevent the loss of weight of these glands observed during prolonged administration of cortisone [8, 9]. We know from the literature that the function of the system of the hypophysis and adrenals is closely related to the activity of the hypothalamus, by means of which the central nervous system exerts its regulatory influence on the function of the hypophysis [1, 6, 7, 11, 13, 14]. Several authors have stressed the significance of the neurosecretory influences of the hypothalamus on the hypophysis [6, 7, 13].

In the present investigation the effect of ethylnorantifein on the neurosecretory processes in the hypothalamus and hypophysis was studied. The action of ethylnorantifein was also studied on the secretion of antidiuretic and adrenocorticotropic hormones, i.e., the effect of the preparation on the activity of the functions of the hypophysis, closely connected with the hypothalamus.

EXPERIMENTAL METHOD

The first part of the investigation was carried out on 24 male albino rats weighing 180-240 g, divided into two groups. The control animals received intraperitoneal injections of physiological saline (0.5 ml), the experimental animals—of ethylnorantifein (20 mg/kg). All the rats were decapitated 2 h after injection of the solutions. The hypothalamus and hypophysis were extracted and fixed in Bouin's fluid. Paraffin wax sections were cut to a thickness of 5-7 μ, stained with paraldehyde-fuchsin by the Gomori-Gabe method, and counterstained by Heidenhain's method.

In the second part of the investigation 36 male rats (180-210 g) were used, and these also were divided into two groups. The control rats received water heated to 30° (5% of the body weight) through a gastric tube. The other group of rats received an intraperitoneal injection of ethylnorantifein (20 mg/kg) 5 min before the injection of water. Every hour for 4 h the diuresis of the animals of both groups was measured. The effect of ethylnorantifein on the secretion of the antidiuretic hormone of the neurohypophysis [4] was judged by the difference between the volumes of urine excreted by the control and experimental rats.

The concentration of 17-hydroxycorticosteroids was determined by the method of N. A. Yudaev and Yu. A. Pankov [10] in plasma (1.5 ml) from blood taken from the hearts of guinea pigs in a long-term experiment before

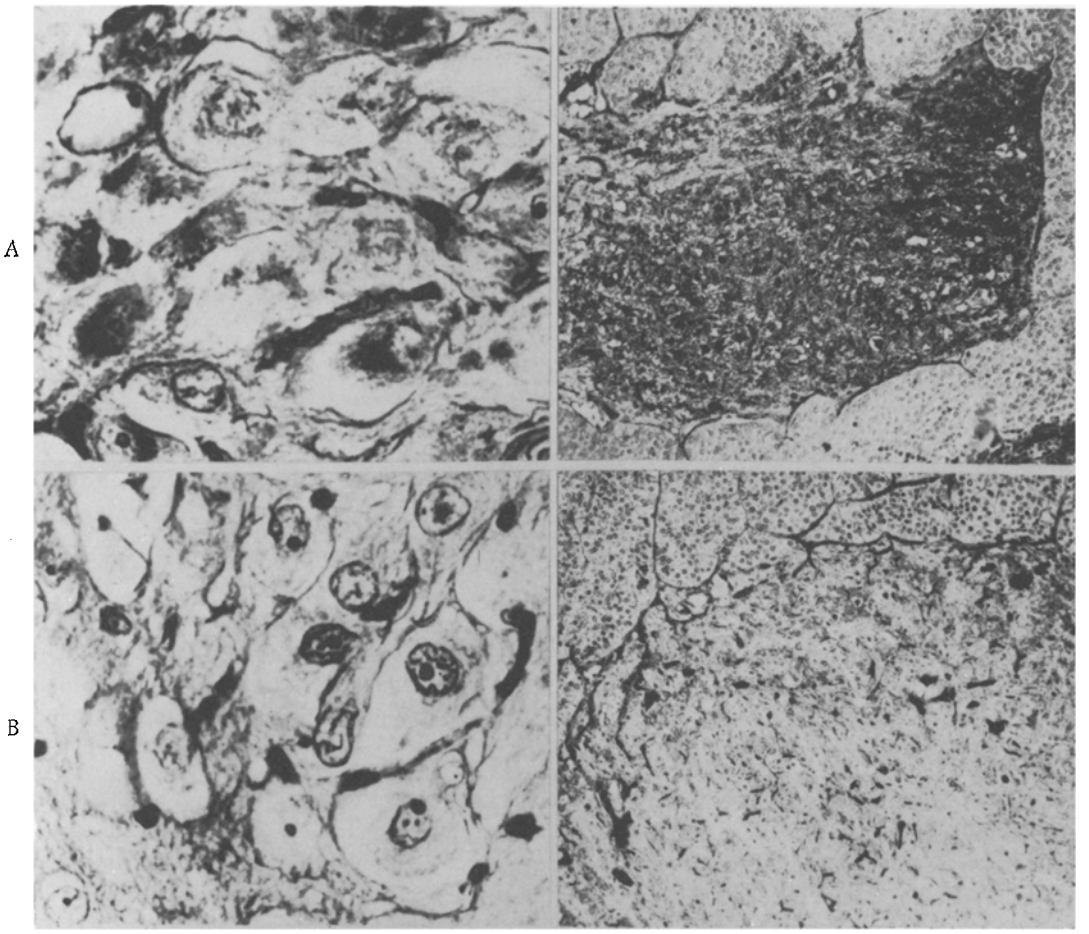

Fig. 1. Supraoptic nuclei of hypothalamus (1) and neurohypophysis (2) of albino rats. A) Control; B) after injection of ethylnorantifein; 1) 800 ×, 2) 116×. Stained with paraldehyde-fuchsin and by Heidenhain's azan method.

and 2-4 h after intraperitoneal injection of ethylnorantifein (20 mg/kg). Removal of the hypophysis from the guinea pigs was undertaken by the method described by Good and co-workers [12].

In the dose used (20 mg/kg), ethylnorantifein caused no visible changes in the behavior of the rats and guinea pigs. The animals reacted more briskly than the controls (pricked up their ears, gave a start, jumped) only in response to a loud sound or to intensive stimulation of the skin.

EXPERIMENTAL RESULTS

Investigation of sections of the hypothalamus (region of the supraoptic nucleus) and hypophysis (posterior lobe) of the control rats (Fig. 1) revealed that the neurons of the supraoptic nucleus were of different sizes and shapes, and that their nuclei and nucleoli were clearly stained. A high concentration of Gomoripositive granules was observed in the smaller cells, in which the secretory granules were arranged perpendicularly and compactly. The nuclei of the large, lightly stained cells were slightly deformed, and the secretory granules were large and dispersed. In some fields of vision capillaries were observed among the cells.

The nerve fibers and their endings in the neurohypophysis of the control rats contained large number of Gomoripositive granules. Frequently large expansions were observed, filled with secretory material and spherical in shape (Hering bodies).

After injection of ethylnorantifein the following changes were found in the hypothalamus and the posterior lobe of the hypophysis (Fig. 1).

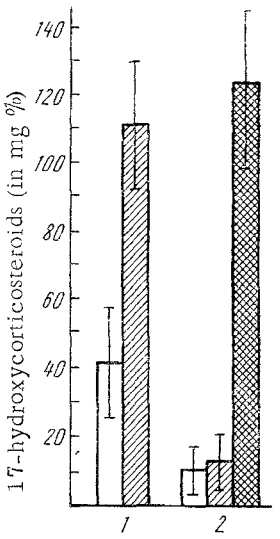

Fig. 2. Concentration of 17-hydroxycorticosteroids in heart blood of guinea pigs. 1) Intact (22 animals); 2) hypophysectomized (16 animals); unshaded column—before administration; obliquely shaded column—2 h after injection of ethylnorantifein; cross-shaded column—2 h after injection of 5 units ACTH.

In the supraoptic nucleus the neurons were large and lightly stained. Their cytoplasm was friable and no secretory granules could be distinguished. Often cells could be seen in which the nuclei were not clearly outlined, consisting of amorphous masses with barely distinguishable nucleoli. In the posterior lobe of the hypophysis the amount of neurosecretion was greatly diminished. No Gomori-positive granules were observed in the terminal expansions. Most of the Hering bodies were empty and only here and there were secretory granules present in the endings of the nerve fibers and their plexuses. Both in the supraoptic nuclei and in the posterior lobe of the hypophysis of the rats marked hyperemia was observed after the administration of ethylnorantifein (Fig. 1).

These results show that, under the influence of ethylnorantifein, the amount of neurosecretion reaching the blood stream from the supraoptic nuclei of the hypothalamus and the posterior lobe of the hypophysis was increased. This conclusion was confirmed by the results of a study of the action of ethylnorantifein on the secretion of antidiuretic hormone by the neurohypophysis of rats after a water load. Four hours after the administration of water to the control rats, for instance, the animals had excreted in their urine 92 ± 6.7% of the total volume of fluid. After the injection of ethylnorantifein, only 38.7 ± 4.3% of the water administered to the rats was excreted in the urine over the same period, so that a considerable inhibition of diuresis was observed.

In the same dose (20 mg/kg) ethylnorantifein, when given to guinea pigs, led to a clear increase in the concentration of 17-hydroxycorticosteroids in the blood after 2-4 h. This stimulant action of ethylnorantifein was not observed in hypophysectomized animals (Fig. 2).

The results of these experiments demonstrate that ethylnorantifein stimulates the secretion of antidiuretic and adrenocorticotropic hormones. This stimulation is associated with an increase in the output of neurosecretion from the hypothalamus.

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