ROLE OF THE CHOLINERGIC AND ADRENERGIC SYSTEMS OF THE HYPOTHALAMUS IN THE REGULATION OF PITUITARY ADRENOCORTICOTROPHIC FUNCTION

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In experiments on male rats the activity of the pituitary-adrenal system was studied after electrolytic destruction of different parts of the hypothalamus. Pharmacological analysis demonstrated the irregular distribution of cholinergic and adrenergic systems controlling the secretion of ACTH and glucocorticoids in the hypothalamus. It is suggested that the cholinergic systems are located in the mammillary region, α-adrenergic systems in the region of the anterior or posterior hypothalamus, and β-adrenergic receptors in the region of the ventromedial nuclei of the hypothalamus. The latter perhaps play an inhibitory role.

KEY WORDS: hypothalamus; corticosteroids; cholinergic and adrenergic systems.

According to data in the literature the pituitary adrenocorticotrophic function is controlled not by an independent center, but by a diffuse nerve net in the ventral part of the hypothalamus; the most effective zone, injury to which inhibits adrenal function, lies in the anteromedial part of the hypothalamus, including the paraventricular and dorsomedial nuclei [1, 11].

Information has been published on the role of the cholinergic and adrenergic structures of the hypothalamus in the regulation of the pituitary–adrenal cortex system [14, 15]. Some workers have attached great importance to these mediator systems [14], whereas others consider that the direct role of cholinergic mediation in the transmission of stimuli to the hypophyseotrophic zone is debatable [15]. It has also been suggested that adrenergic structures have an inhibitory effect on ACTH secretion [12].

The object of this investigation was to study the possible localization of cholinergic and adrenergic systems of the hypothalamus which participate in the regulation of the functional activity of the pituitary–adrenal cortex system.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 180-200 g. As a first step, under amobarbital anesthesia (70 mg/kg), electrocoagulation of various zones of the hypothalamus was carried out (current 2 mA, duration 20 sec) through a metal electrode with glass insulation. Depending on the localization of the region of destruction the animals were divided into four groups. The region of the anterior hypothalamic nuclei was destroyed in group 1, the ventromedial nuclei in group 2, the mammillary region in group 3, and the animals of group 4 underwent a mock operation. The site of the foci of electrolytic destruction of the hypothalamic structures was verified in each animal at the end of the experiment by comparing brain sections with the atlas [13].

The drugs for testing were injected intraperitoneally 10 days after the operation; the nicotinic cholinomimetic anabazin [2-(3-pyridyl)piperidine] hydrochloride was injected in a dose of 2 mg/kg [10]; the muscarinic cholinolytic metamizil (methyldiazine) in a dose of 7 mg/kg; the compound fepracet, with α-adrenoblocking properties [3] in a dose of 25 mg/kg, and the β-adrenolytic inderal (propranolol) in a dose of 10 mg/kg. The animals were decapitated 1 h after injection of the drugs and blood was collected; the concentration of 11-hydroxycorticosteroids (11-HCS), reflecting the activity of the hypothalamic-hypophyseo-adrenal system, was

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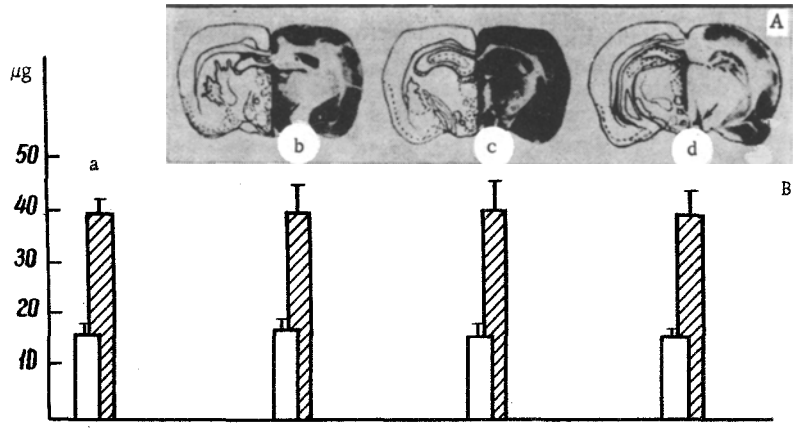

Fig. 1. Localization of hypothalamic injuries (A) and response of pituitary-adrenal system to nociceptive stimulation (B). Arrows on sections indicate site of coagulation. Columns represent 11-HCS concentration in blood plasma (in μg %): unshaded column – control, shaded column – after injection of formalin; a) rats undergoing mock operation; b) with injury to anterior hypothalamus; c) with injury to ventromedial hypothalamus; d) with injury to posterior hypothalamus.

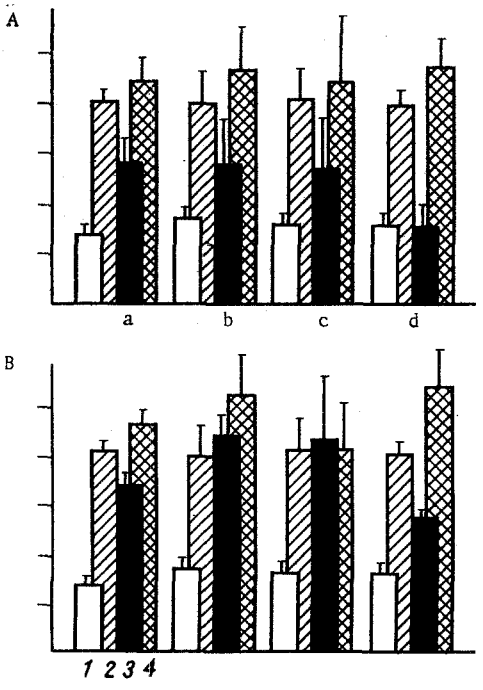

Fig. 2

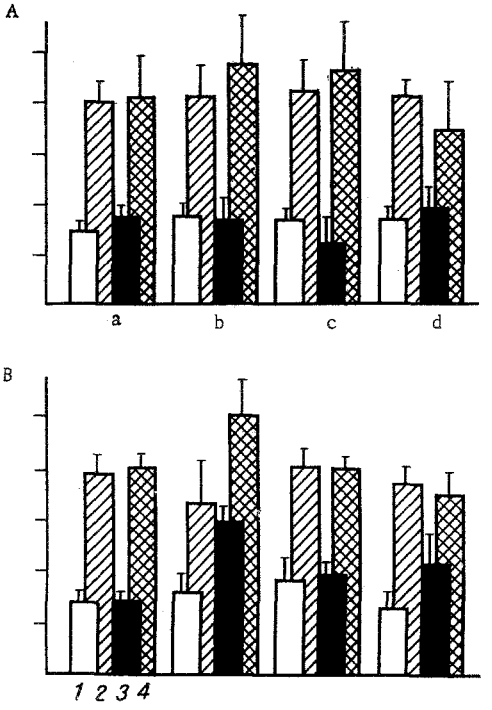

Fig. 3

Fig. 2. 11-HCS concentration in peripheral blood plasma after injection of anabazin (A) and metamizil (B). Columns represent concentration of corticosteroids (in μg %) in animals undergoing mock operation (a), after electrocoagulation in region of anterior (b), middle (c), and posterior hypothalamus (d). 1) Control; 2) loading (formalin); 3) after injection of drug; 4) drug+loading.

Fig. 3. 11-HCS concentration in peripheral blood plasma after injection of fepracet (A) and inderal (B). Remainder of legend as in Fig. 2.

determined in the blood plasma fluorometrically [9]. To activate the pituitary–adrenal cortex system some animals of each group were subjected to nociceptive stimulation (injection of 0.1 ml of 10% formalin solution beneath the plantar aponeurosis) 30 min before sacrifice of the rats.

The results were subjected to statistical analysis [2].

EXPERIMENTAL RESULTS

Ten days after bilateral electrocoagulation the corticosteroid level in the peripheral blood plasma of the animals undergoing the operation in the various groups did not differ significantly from that in the rats undergoing the mock operation (Fig. 1). Local electrolytic destruction in the region of the nuclei of the anterior, middle, or posterior hypothalamus evidently is not reflected in functional activity of the pituitary–adrenal complex, confirming the data of other workers [11, 12] who observed no effect from single destructive foci in the hypothalamus on the basal level of ACTH secretion. It must be pointed out that in animals with destruction in the region of the anterior hypothalamic, ventromedial, and mammillary nuclei injection of formalin increased the plasma 11-HCS concentration by the same amount compared with rats of the control group, possible evidence also in support of the above-mentioned hypothesis.

It is stated in the literature that substances exciting cholinergic structures activate the adrenocorticotrophic function of the pituitary [6, 7, 10]. In the present experiments with the nicotinic cholinomimetic anabazin, a significant increase ($P < 0.001$) in the corticosteroid level also was observed 1 h after injection of the drug in the animals undergoing the mock operation. Destructive lesions in the region of the anterior hypothalamic or ventromedial nuclei did not weaken the stimulating action of the drug. Meanwhile in rats with electrocoagulation of the zone of the mammillary nuclei injection of anabazin did not cause any increase in the steroid concentrations (Fig. 2A).

Cholinergic endings are known to be concentrated in the region of the anterior zone, the mammillary nuclei, and the lateral part of the hypothalamus, whereas its ventral zone contains hardly any cholinergic structures [15]. Since local electrocoagulation in the posterior hypothalamic zone prevents an increase in the corticosteroid level in response to injection of anabazin, this suggests that cholinergic mechanisms of this region are in fact concerned in the realization of the activating effect of the drug.

An increase in the blood corticosteroid concentration of the animals undergoing the mock operation also was observed 1 h after injection of the muscarinic cholinolytic metamizil. As Fig. 2B shows, foci of destruction in the region of the anterior hypothalamic or ventromedial nuclei significantly increased the 11-HCS concentration when metamizil was given, whereas local electrocoagulation of the region of the mammillary nuclei weakened the stimulating effect of metamizil, although it did not block it completely as in the experiments with anabazin.

The results show that electrolytic destruction of the region of the mammillary nuclei led to weakening of the response of the hypothalamic-hypophyseo-adrenal system to injection of anabazin or metamizil. This suggests that cholinergic systems located in the posterior part of the hypothalamus play a definite part in the regulation of the secretion of ACTH and glucocorticoids.

Different results were observed when the adrenoblockers fepracet and inderal were used. The blood plasma 11-HCS level was reduced to 11.3 ± 3 μg % 1 h after injection of the α-adrenoblocker fepracet (Fig. 3A) into rats with destruction of the ventromedial region of the hypothalamus (16 ± 1.2 μg % in the control animals). In animals of the other groups, including those undergoing the mock operation, fepracet had no significant effect either on the initial blood corticosteroid concentration or on the response of the pituitary–adrenal complex to injection of formalin. Catecholamine-containing fibers are known to enter the hypothalamus in the composition of the ventral fasciculus and are concentrated in the median eminence and mediobasal part of the hypothalamus [5]. The results now obtained suggest that α-adrenergic neurons participating in the regulation of ACTH secretion are evidently located outside the region of the ventromedial hypothalamic nuclei.

Injection of the β-adrenoblocker inderal (propranolol) led to an increase in the basal blood corticosteroid concentration of the animals with electrolytic lesions in the region of the anterior and posterior hypothalamus (Fig. 3B). It can tentatively be suggested that β-adrenergic neurons of the ventromedial region of the hypothalamus have an inhibitory function on the pituitary–adrenal system, and their blocking by inderal after destruction of the anterior or posterior hypothalamic zones leads to activation of that system. However, this is also shown indirectly by the elevation of the blood corticosteroid level in response to nociceptive stimulation (formalin) after preliminary injection of the β-adrenoblocker in the rats with coagulation of the zone of the anterior hypothalamus. On the other hand, the possibility of a more marked manifestation of cholinergic responses after blockade of the adrenergic mechanisms cannot be ruled out [4].

The results of experiments showing that the response of the pituitary–adrenal cortex system to the stimulus is effective equally after administration of cholinergic and adrenergic blocking agents evidently indicate that their possible role lies mainly in maintaining the tonic phase of secretion of ACTH and glucocorticoids, but not in regulating the adrenocorticotropic function of the pituitary during exposure to an extraordinary stimulus. Meanwhile the data described above confirm the previous hypothesis [8] that other mediator systems of the brain participate in the mechanisms of nervous regulation of functional activity of the pituitary–adrenal complex.

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