ROLE OF THE HYPOTHALAMUS IN INHIBITION OF THE PITUITARY–ADRENOCORTICAL SYSTEM BY A FEEDBACK MECHANISM

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One of the most important principles of control of the hypothalamo-hypophyseo-adrenocortical system is regulation by a feedback mechanism. The role of the hypothalamus in this mechanism is demonstrated by results obtained *in vitro* [4, 5, 11], experiments with implantation of corticosteroids in the hypothalamus [6-8], and changes in ACTH-releasing activity after administration of corticosteroids [4, 10]. The importance of individual hypothalamic structures in the feedback mechanism is not yet clear. Elucidation of the role of the paraventricular and ventromedial nuclei is particularly interesting. We know that these nuclei activate the pituitary–adrenocortical system [2, 3, 9], and recent investigations suggest that neurons producing corticotrophin releasing factor (CRF) are located in the paraventricular nuclei [3, 9, 12-14].

The object of this investigation was to study the role of the paraventricular and ventromedial hypothalamic nuclei in the mechanism of inhibition of the pituitary–adrenocortical system by corticosteroids.

EXPERIMENTAL METHOD

Male chinchilla rabbits were used. Inhibition of the stress reaction of the pituitary–adrenocortical system by hydrocortisone was studied in intact rabbits and after bilateral destruction of the paraventricular or ventromedial hypothalamic nuclei. A reaction of the system was judged from the blood corticosteroid level determined spectrofluorometrically [15]. Immobilization stress was induced by stretching the rabbits by their fore- and hind-limbs. The hypothalamic nuclei were destroyed under pentobarbital anesthesia by a high-frequency current (10 kHz, 10 mA, 60 sec). The electric current was applied through an electrode inserted in accordance with coordinates from a stereotaxic atlas into the paraventricular and ventromedial nuclei. The experiments began 3 weeks after the operation and were conducted on waking rabbits. Blood was taken from the marginal vein of the ear before (5-7 min) and during (at the 30th and 60th minutes) immobilization. Hydrocortisone (100 μg/kg) was injected into the ear vein 5 min before the beginning of stress. A water-soluble form of the hormone was used: cortisol hydrogen succinate (Switzerland). At the end of the experiments the completeness of destruction of the hypothalamic nuclei was confirmed in frontal brain sections. The blood corticosteroid level before immobilization was taken as 100% and hormone concentrations during immobilization were expressed relative to it. From the results of each series of experiments the mean and error of the mean were then determined.

EXPERIMENTAL RESULTS

Intravenous injection of 100 μg/kg hydrocortisone 5 min before the beginning of immobilization led to inhibition of the stress-induced increase in the blood corticosteroid concentration (Fig. 1), in agreement with previous data [1].

Destruction of the ventromedial nuclei led to depression of the response to immobilization (Fig. 1). After destruction the inhibitory effect of the corticosteroids was weakened. The stress reaction of the pituitary–adrenocortical system was inhibited by hydrocortisone less than in intact animals. In rabbits with destruction of the ventromedial nuclei injection

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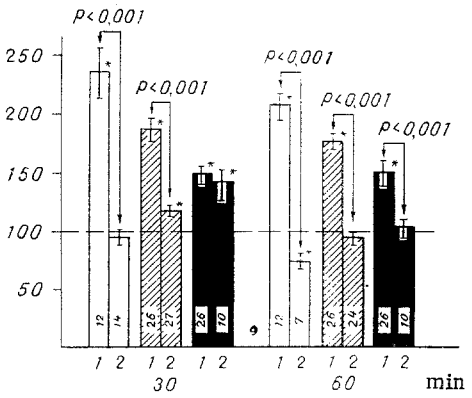

Fig. 1. Effect of hydrocortisone on stress-induced reaction of pituitary—adrenocortical system in intact (I) rabbits and rabbits after destruction of the ventromedial (VM) and paraventricular (PV) hypothalamic nuclei. Abscissa, duration of immobilization; 1) immobilization; 2) immobilization + 100 μg/kg hydrocortisone. Ordinate, plasma corticosteroid concentration (M ± m) (in % of hormone level before immobilization). Numbers at base of columns give number of cases. Asterisk denotes significance of difference from background value at $P < 0.05$ level. Here and in Fig. 2: unshaded columns — intact animals, oblique shading — destruction of ventromedial nuclei, black columns — destruction of paraventricular nuclei.

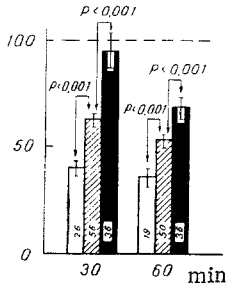

Fig. 2. Degree of inhibition of stress reaction by hydrocortisone in intact rabbits and rabbits with destruction of ventromedial and paraventricular hypothalamic nuclei. Hormone level during immobilization in animals not receiving hydrocortisone taken as 100%. Abscissa, duration of immobilization (hydrocortisone injected 5 min before beginning of stress). Ordinate, plasma corticosteroid level (in %; M ± m). Numbers near foot of columns denote number of cases.

of hydrocortisone did not evoke the depression of the stress level of corticosteroids which it did in intact animals (Fig. 1). In rabbits given hydrocortisone the blood corticosteroid level at the 30th minute of immobilization was higher than in intact animal ($P < 0.05$), and at the 60th minute it was not lower than initially, although in intact rabbits the corticosteroid level at this time had fallen below the background value (Fig. 1). Depression of the inhibitory effect of the synthetic corticosteroid analog dexamethasone after destruction of the ventromedial hypothalamic region was demonstrated previously [2].

Destruction of the paraventricular hypothalamic nuclei led to weakening of activation of the pituitary—adrenocortical system evoked by immobilization. After destruction of these nuclei there was a marked decrease in the inhibitory action of hydrocortisone. At the 30th minute of immobilization hydrocortisone did not cause inhibition of the stress reaction, but at the 60th minute the corticosteroid level fell, although it still remained higher than in intact animals (Fig. 1).

The degree of inhibition of the stress reactions in rabbits with an intact brain and with destruction of the paraventricular and ventromedial nuclei is compared in Fig. 2. Clearly the highest degree of inhibition was observed in intact rabbits.

Destruction of the ventromedial nuclei leads to lessening of inhibition. After destruction of the paraventricular nuclei inhibition decreased even more and differed significantly

from inhibition of the stress reaction observed in animals with destruction of the ventromedial nuclei (Fig. 2).

The results are evidence that both the paraventricular and the ventromedial hypothalamic nuclei are essential for normal inhibition of the pituitary–adrenocortical system by a negative feedback mechanism. The paraventricular nuclei play an important role in the mechanism of inhibition of the system. Inhibition of pituitary–adrenocortical function may take place through the direct action of the hormone on the regions studied or through the action of the hormone on structures from which pathways pass through the paraventricular and ventromedial nuclei.

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