MECHANISM OF ACTION OF RESERPINE ON THE PITUITARY — ADRENAL CORTEX SYSTEM

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Reserpine lowers the noradrenalin concentration in the hypothalamus and changes the reactivity of the adrenocorticotropic function of the pituitary in response to stress.

According to reports in the literature [1, 4–10, 18, 19], monoamines of the central nervous system (especially of the hypothalamus) possibly play a role in regulating the adrenocorticotropic (ACT) function of the pituitary. Conclusions that catecholamines (CA) of the hypothalamus participate in regulation of pituitary ACT function were based on experiments with reserpine, a substance exhausting monoamine reserves in the tissues, and are highly contradictory [2, 9-12, 14, 17]. The reason for this is that the compound was given by different methods and in different doses, and different tests were used to assess the results at different times.

In this investigation the CA level in the hypothalamus and the ACT function of the pituitary was found to be mutually dependent.

EXPERIMENTAL METHOD

Noninbred male rats weighing 160-200 g were used. The animals of 4 experimental groups received 0.2 and 2 mg/kg reserpine (Rausidil, Gedeon Richter, Hungary) by intramuscular injection, while the animals of 4 control groups received physiological saline in the same volume. The animals were sacrificed 3 and 24 h after injection of the preparations. Plasma and pituitary ACT activity was determined by the biological method of Vernikos and Danellis in V. M. Rozental's modification, and the adrenalin (A) and noradrenalin (NA) concentrations in the plasma, adrenals, and hypothalamus were determined by the fluorimetric method of Euler and Lishaiko as modified by Matlina [3].

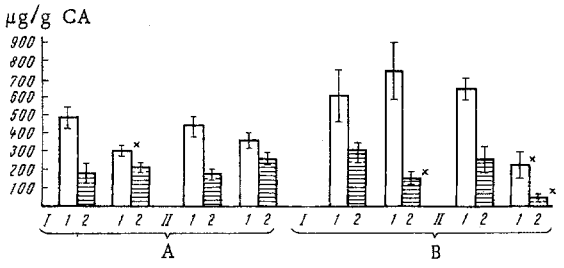

Fig. 1. Action of physiological saline (1) and reserpine (2) in doses of 0.2 mg/kg (A) and 2 mg/kg (B) on concentration of adrenalin (unshaded columns) and noradrenalin (shaded columns) in adrenals 3 (I) and 24 (II) h after injection. x) Denotes significant differences.

Besides these experimental groups, a further 16 groups were used, consisting of animals receiving reserpine and physiological saline as described above but subjected additionally to the action of combined stress. The animals of 8 of these groups were sacrificed 15-20 sec after laparotomy for analysis of CA in the hypothalamus, and the other animals were sacrificed 2.5 min after laparotomy for analysis of the ACT activity of the blood and pituitary.

EXPERIMENTAL RESULTS

Injection of reserpine in a dose of 0.2 mg/kg reduced the A concentration in the adrenals, but only

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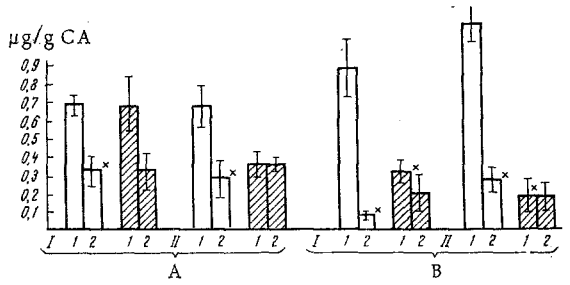

Fig. 2

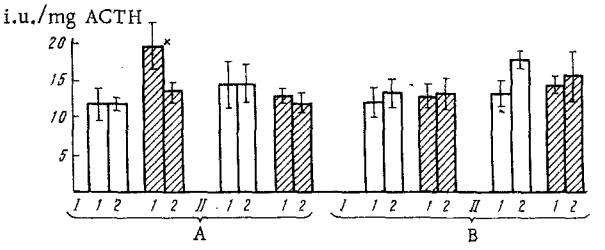

Fig. 3

Fig. 2. Action of reserpine in dose of 0.2 mg/kg (A) and 2 mg/kg (B) on basal concentration of noradrenalin (1) and noradrenalin concentration after action of stress (2) 3 (I0 and 24 (II) h after injection of physiological saline (unshaded columns) and reserpine (shaded columns); x) denotes significant differences.

Fig. 3. Action of reserpine in dose of 0.2 mg/kg (A) and 2 mg/kg (B) on basal ACTH level (1) and on ACTH level after exposure to stress (2) 3 (I) and 24 (II) h after injection of physiological saline (unshaded columns), and of reserpine (shaded columns); x) denotes significant differences.

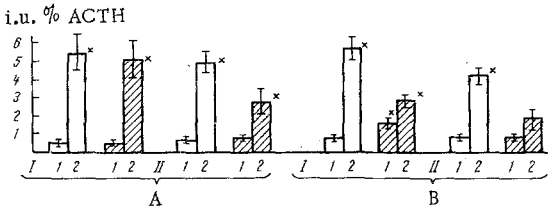

Fig. 4. Action of reserpine in dose of 0.2 mg/kg (A) and 2 mg/kg (B) on basal secretion of ACTH (1) and on secretion of ACTH in response to stress (2) 3 (I) and 24 (II) h after injection of physiological saline (unshaded columns) and of reserpine (shaded columns); x) denotes significant differences.

after 3 h, without any change in its concentration in the peripheral blood (Fig. 1A). With an increase in the dose of reserpine to 2 mg/kg, the exhausting action of the compound on the A concentration in the adrenals reached a maximum after 24 h, and the effect was more marked; in this case no A could be found in the blood by the methods used. The NA level was reduced after both 3 and 24 h, while its blood concentration remained unchanged (Fig. 1B).

The NA concentration in the hypothalamus 3 h after injection of the small dose of reserpine was unchanged, while 24 h after injection it was reduced to 54.3% of the control; no significant changes in the A concentration were observed (Fig. 2A). The NA level in the hypothalamus was sharply reduced by the action of the larger dose of reserpine, and the exhausting action of the drug was apparent 3 h after its injection (Fig. 2B).

The writer [7] has shown previously that the action of stress on intact animals produces after 15-20 sec a sharp decrease in the NA concentration in the hypothalamus. It was therefore interesting to examine whether the action of stress on rats receiving reserpine would produce a decrease in the NA concentration in the hypothalamus, the normal response of intact animals.

The results showed that a direct relationship exists between the degree of lowering of the NA level in the hypothalamus and the initial NA level in that structure. Characteristically, the presence or absence of lowering of the NA concentration in the hypothalamus after stress was independent of the initial CA level in the adrenals (compare Figs. 1A, B, and 2A, B).

An increase in the ACTH level in the pituitary was observed 3 h after injection of 0.2 mg/kg reserpine, without any changes in its secretion, possibly indicating increased synthesis of the hormone in the gland (Figs. 3A, 4A). A dose of reserpine 10 times greater caused a marked increase (by 2.3 times) in the blood ACTH concentration 3 h after injection, without any changes in the pituitary ACTH level, thus indicating an increase not only in secretion of the hormone, but also in its synthesis, for otherwise increased secretion of the hormone must have led to exhaustion of the ACTH reserves in the gland (Figs. 4B and 3B). Normal levels were restored after 24 h.

The action of stress 3 h after injection of the smaller dose of reserpine caused a normal reaction of liberation of ACTH with no changes in its concentration in the pituitary, which evidently must indicate a fresh increase in the intensity of synthesis of the hormone (Figs. 3A and 4A). Stress also produced libera-

tion of ACTH from the pituitary 24 h after administration of the same dose of the drug. However, the degree of liberation of the hormone in the "reserpinized" rats was much lower than in the controls (Fig. 4A).

The larger dose of reserpine 3 h after injection reduced to one-eighth the reaction of liberation of ACTH from the pituitary, without reducing its concentration in the gland. In the same dose, 24 h after injection, no ACTH was liberated from the pituitary in response to stress. The ACTH level in the pituitary still remained unchanged, perhaps indicating a decrease in the intensity of synthesis of the hormone in the gland (Figs. 3B and 4B).

Hence, in the doses tested, during the first 3 h after its injection reserpine stimulates the ACT function of the pituitary. This agrees with the results of previous investigations [9, 12, 13]. No subsequent depression of the basal secretory ACT activity of the pituitary was found. However, the reaction of the pituitary to stress was modified. Liberation of ACTH from the pituitary into the blood stream was reduced or absent, in agreement with other observations [12, 13, 16]. In the present experiments the degree of decrease in liberation of ACTH from the pituitary in response to stress was directly dependent on the dose of the compound and independent of the initial blood hormone level. It must be specially emphasized that, unlike Kitay and co-workers, Saffzan and Vogt, and Maickel and co-workers [12, 13, 15], no exhausting action of reserpine on the pituitary was found. Consequently, in this case it cannot be concluded that the cause of the disturbance of pituitary reactivity in response to stress is exhaustion of the ACTH content in the gland.

Comparison of data for the action of reserpine on the CA concentration in the hypothalamus and adrenals, on the one hand, and on the ACTH level on the other hand suggests that changes in reactivity of the ACT function of the pituitary in "reserpinized" rats in response to stress are directly dependent on the presence or absence of a decrease in the NA concentration in the hypothalamus under these conditions. The presence or absence of a decrease in NA concentration in response to stress in the hypothalamus is determined, however, by its initial level. This reaction and, consequently, the liberation of ACTH from the pituitary in response to stress are independent of the initial CA concentration in the adrenals and of the level of basal secretion of ACTH. It is determined entirely by the possibility of an instantaneous fall in the NA concentration in the hypothalamus in response to stress. However, to maintain the basal level of ACTH secretion, minimal reserves of NA in the hypothalamus are probably adequate. It can also be assumed that maintenance of the basal ACTH secretion is independent of the NA level in the hypothalamus. This conclusion was reached by Hirch and Moor from their investigations [11]. However, these workers unjustifiably deny that the ACT function of the pituitary is dependent on the CA concentration in the hypothalamus.

Comparison of the action of reserpine on the ACTH levels of the pituitary and blood suggests that NA mainly regulates the secretory function of the pituitary in response to stress.

Experiments with reserpine thus confirmed the writer's previous hypothesis [7, 8] that monoamines (in this case, NA) of the hypothalamus play an important role in regulation of the ACT function of the pituitary. However, NA of the hypothalamus participates in regulation of the pituitary ACT function only during the action of extreme factors. In a resting state the ACT function (basal secretion) clearly is independent of NA, and in precisely the same way the basal level of ACTH secretion was not determined by the action of the gland in response to extreme stimuli. The degree of response of the pituitary to unfavorable conditions depends entirely on the reactivity of the monoaminergic (including adrenergic) structures of the hypothalamus.

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