THE USE OF DOPA IN REPLACEMENT THERAPY IN DISTURBANCES OF CIRCULATORY REGULATION DURING STRESS

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Changes in the noradrenalin level in the hypothalamus were studied in cats and compared with the state of sympathetic and vasomotor tone during a response to stress produced by injection of 0.25 M KCl solution into the lateral ventricles. In phase 1 of the stress reaction (activation of the sympathico-adrenal system) no significant changes took place in the noradrenalin concentration in the hypothalamus. In phase 2 of the response to stress inhibition of sympathetic and vasomotor tone was accompanied by a significant decrease in the noradrenalin concentration in the hypothalamus. DOPA (20-40 mg/kg) restored the total noradrenalin concentration in the hypothalamus during stress and led to increased sympathetic and vascular tone and restoration of the normal level of the arterial pressure.

The important role of the sympathico-adrenal system in the development of pathological responses of the circulation to stress is well-known [10]. It has also been shown that central adrenergic mechanisms, as well as peripheral, participate in the disturbance of circulatory regulation [4, 5]. The adrenergic systems of the hypothalamus, controlling the degree of irradiation of excitation in the arcs of the vasomotor reflexes may have a significant part to play [3, 11].

In this investigation changes in the noradrenalin concentration in the hypothalamus in cats were compared with the state of sympathetic and vasomotor tone during stress and under the influence of DOPA.

EXPERIMENTAL METHOD

To reproduce a neurogenic stress response in cats, 0.25 M KCl solution was injected into their lateral ventricles [1]. Tonic and reflex activity in the sympathetic nerves of the heart and kidneys [6], the arterial pulse pressure in the femoral and carotid arteries, and the ECG were recorded in animals anesthetized with urethane and chloralose. Recordings were carried out on the Elema Mingograph-81 instrument. Noradrenalin in the hypothalamus, including the preoptic region and mammillary bodies, was determined on an Opton spectrofluorometer by the method of Von Euler and Lishajko [8] in Men'shikov's modification [7]. Noradrenalin was determined in the hypothalamus of the intact animals and 15-20 min (phase 1 of the stress reaction) and 90-120 min (phase 2 of the stress reaction) after the injection of KCl. The effect of DOPA on the noradrenalin concentration in the hypothalamus also was studied 90-120 min after the injection of KCl. DOPA was injected intravenously in fractional doses of 5 mg/kg at intervals of 5-10 min (total dose 20-40 mg/kg). At least six animals were used in each series of experiments.

EXPERIMENTAL RESULTS AND DISCUSSION

It was shown previously that injection of KCl into the lateral ventricles leads to two qualitatively different phases of cardiovascular responses in cats. The first phase is characterized by a considerable

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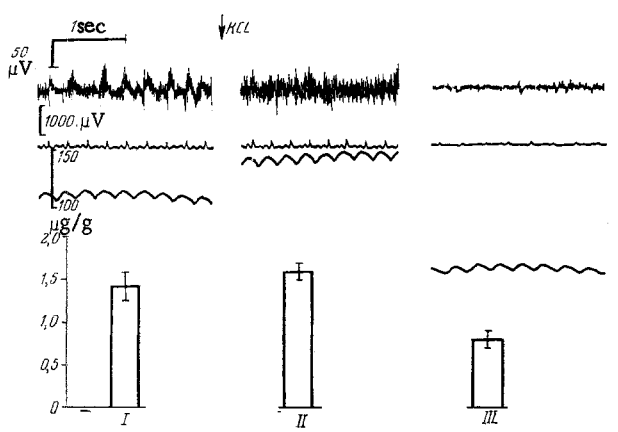

Fig. 1

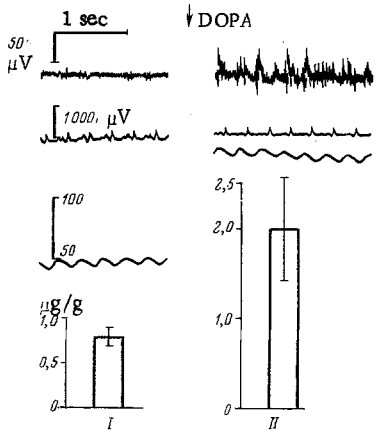

Fig. 2

Fig. 1. Effect of injection of KCl into lateral ventricles on tonic activity in renal sympathetic nerve, ECG, arterial pressure, and noradrenalin concentration in hypothalamus of cats from top to bottom: calibration (50 μV, 1 sec), tonic activity in renal sympathetic nerve, calibration (1000 μV), ECG, arterial pulse pressure, noradrenalin concentration in hypothalamus (in μg/g tissue): I) control; II) 20 min after injection of KCl; III) 120 min after injection of KCl.

Fig. 2. Effect of DOPA on noradrenalin concentration in hypothalamus, tonic activity in renal sympathetic nerve, and arterial pressure after injection of KCl. From top to bottom: tonic activity, ECG, arterial pressure, and noradrenalin concentration in hypothalamus: I) phase 2 of stress response without DOPA; II) the same in experiments with DOPA.

increase of activity in the sympathetic nerves, culminating in acute disturbances of the coronary circulation and cardiac activity accompanied by elevation of the arterial pressure to 220-240 mm Hg. These disturbances can be abolished by desympathization or by adrenolytic drugs. The second phase is characterized by a decrease of activity in the sympathetic nerves, vasodilatation, venous stasis, hypotension, and bradycardia [2].

The results of the present experiments showed that the mean noradrenalin concentration in the hypothalamus of the control cats was 1.45 ± 0.13 μg/g tissue. In phase 1 of the stress response, i.e., during activation of the sympathico-adrenal system (for 15-20 min after administration of KCl) the noradrenalin concentration in the hypothalamus was virtually unchanged (1.59 ± 0.13 μg/g).

In the period of depression of sympathetic tone and vasomotor reflexes and also of a marked lowering of arterial pressure (to 60-40 mm) 90-120 min after injection of the KCl a marked decrease in the noradrenalin concentration was observed in the hypothalamus (0.81 ± 0.09 μg/g; $P < 0.001$; Fig. 1).

It is important to note that exhaustion of the endogenous reserves of noradrenalin in the hypothalamus produced by reserpine (0.5-1.0 mg/kg) also was accompanied by depression of tonic and reflex activity in the sympathetic nerves and by a lowering of vascular tone.

Intravenous injection of DOPA restored the total noradrenalin concentration in the hypothalamus in phase 2 of the stress response (1.98 ± 0.61 μg/g). The sympathetic tone was raised, the normal arterial pressure was restored (Fig. 2), and reflex responses in the sympathetic nerves and pressor vasomotor reflexes reappeared.

These results show that maintenance of a definite level of noradrenalin in the hypothalamus is an important condition for the normal function of the brain centers controlling the circulation.

The decrease in the noradrenalin concentration in the hypothalamus in phase 2 of the stress response evidently signifies not the inhibition of noradrenalin synthesis but, on the contrary, activation of its synthesis for DOPA restored the level of this mediator. Exhaustion of the noradrenalin reserves in the hypothalamus was evidently connected with its increased liberation and metabolism. This conclusion is con-

firmed by other observations [9, 11] showing that the lowering of the noradrenalin level in the brain, especially in the hypothalamus, during stress is accompanied by an increase in O-methylated products. The rapid restoration of the noradrenalin level under the influence of DOPA is evidence of a deficiency of precursors of the mediator. This view is supported by data in the literature showing a decrease in the blood and tissue levels of dopamine and DOPA in stress.

These results suggest that DOPA can be used as an agent in replacement therapy during stress reactions.

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