

BIOPHYSICS AND BIOCHEMISTRY

Possible Contribution of Epiphyseo-Adrenocortical Relations to Antidepressive Effect of Imipramine

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Chronically administered of imipramine decreases, while the depressogen reserpine increases, the level of plasma corticosterone in rats. The only effect of reserpine is antidepressive. Epiphysectomy stimulates the endocrine response to reserpine and attenuates the antireserpine effect of imipramine. This may be caused by antidepressive effect of epiphyseal factors.

Key Words: *imipramine; reserpine; epiphysis; adrenocortical system*

Endocrine disorders caused by hypothalamo-pituitary-adrenocortical defects are a pathogenetic factor of mental depression. These disorders increase glucocorticoid level and deteriorate emotogenic activity of the brain [5,7]. The function of the hypothalamo-pituitary-adrenocortical system depends on the activity of cerebral epiphysis, whose main hormone melatonin exhibits antidepressive activity [1,2]. We studied the effects of antidepressants on secretory processes in the adrenal cortex of epiphysectomized rats in a state of depression as exemplified by imipramine (IP). These studies will provide information on the role of epiphyseo-adrenocortical relations in the specific effect of the drug.

MATERIALS AND METHODS

Experiments were carried out in spring and summer (April-June) on 60 outbred albino rats weighing 100-120 g. Corticosterone in 0.1 ml blood plasma was measured by fluorometry (micromodification [4]) in a Hitachi spectrophotometer at 475 nm (for fluorescence stimulation) and 530 nm (distinguishing the maximum fluorescence spectra).

Two series of experiments were carried out. The first series was performed on 4 groups of animals, 6 per group: 1) animals were repeatedly injected with normal saline intraperitoneally, as all the drugs, and in the same volume (control); 2) chronic IP in a daily dose of 10 mg/kg for 14 days; 3) reserpine in a single dose of 2 mg/kg 24 h before measurement; and 4) reserpine+IP (on the day of the last injection of antidepressant). In the second series we evaluated endocrine shifts after resection of the epiphysis by a method modified at our laboratory or after a sham operation (trephination without removing the gland). Fifteen rats were subjected to each operation, and 2 weeks after the intervention these rats were divided into 3 subgroups, 5 animals in each: 1) chronic IP, 2) single dose of reserpine, and 3) IP and reserpine. Control group for this series consisted of 5 intact rats.

All animals were maintained under standard vivarium conditions on standard diet with free access to fodder and water at natural illumination. The results were statistically processed using Student's *t* test.

RESULTS

Plasma corticosterone level in the controls injected with normal saline was higher than in animals not subjected to stress caused by injections. Acute ad-

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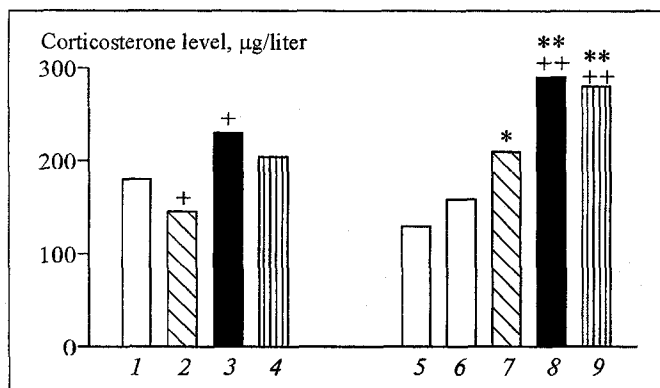


Fig. 1. The effect of epiphysectomy on shifts in plasma corticosterone content induced by imipramine (IP) and reserpine in rats. 1) normal saline; 2) IP (10 mg/kg, 14 days); 3) reserpine (2 mg/kg); 4) reserpine+IP; 5) intact rats; 6) epiphysectomized animals; 7) IM (10 mg/kg, 14 days) after epiphysectomy; 8) reserpine (2 mg/kg) after epiphysectomy; 9) reserpine+IP after epiphysectomy. * $p < 0.05$, ** $p < 0.001$ vs. intact rats; * $p < 0.01$, ** $p < 0.001$ vs. rats injected with normal saline.

ministration of IP did not alter, while chronic IP significantly decreased the hormone concentration in the blood (Fig. 1). After reserpine in a dose augmenting the depression (according to our behavioral studies) secretory activity of adrenal cortex increased. This agrees with the data of others on stable hypercorticalism under the effect of reserpine [6].

Epiphysectomy did not significantly affect plasma content of corticosterone; there was a negligible tendency to an increase in adrenocortical secretion. Sham operations induced no shifts either. Therefore, normally, epiphyseal regulation of adrenocortical activity is insignificant, which agrees with published reports [2]. On the other hand, epiphysectomy modified endocrine response to IP, which did not decrease but increased the hormone level in comparison with intact controls, probably because of the absence of epiphyseal melatonin limiting adrenocortical activity [3]. By blocking the noradrenalin return by sympathetic neurons innervating the epi-

physis, IP stimulated melatonin synthesis in this gland [3]. Melatonin inhibits the metabolism of the cerebral stem catecholamines that inhibit the secretion of hypothalamic corticotropin releasing hormone [6,10].

Epiphyseal deficiency potentiated the effect of reserpine. Plasma hormone content increased to 298 ± 22 µg/liter vs. 229 ± 37.6 µg/liter after reserpine alone. This shift is probably determined by the capacity of reserpine to provoke complex disorders in noradrenergic limiting regulation of corticotropin releasing hormone production and in sympathetic regulation of the gland function [9]. The antireserpine effect of IP is virtually null under such conditions (Fig. 1). Nevertheless, this effect is retained in sham operated animals with corticosterone level 163 ± 30 vs. 289 ± 19.5 µg/liter after epiphysectomy.

Therefore, epiphyseal factors contribute to the IP capacity to limit corticosterone secretion. This effect may modify specific antidepressive activity of the drug, because after epiphysectomy IP did not decrease hypercorticalism caused by the depressogenic agent.

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