PRENATAL MODIFICATION OF ADRENOCORTICAL FUNCTION OF ADULT RATS WITH HEREDITARY ARTERIAL HYPERTENSION BY HYDROCORTISONE

N. N. Dygalo, A. L. Markel',
and E. V. Naumenko

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A decisive role in the formation of hereditarily determined hypertension in rats is played by increased sympathetic nervous activity during the early period of development, linked with the pattern of central noradrenergic regulation of its tone [3]. In turn, the formation of noradrenalin mechanisms of the young rat brain during development depends on the maternal blood corticosteroid level during pregnancy [2]. Elevation of the blood corticosteroid level in pregnant normotensive females changes the noradrenergic system of the brain and the reactivity of the pituitary-adrenal complex in the adult progeny during exposure to emotional stress [7, 8]. The modifying action of glucocorticoids in the period of intrauterine development depends on the hereditary characteristics of the animals [3]. Meanwhile we know that reactivity to stress is an important factor in the pathogenesis of essential hypertension [4, 5, 10].

The aim of this investigation was to study the effect of an increased glucocorticoid concentration during intrauterine development on reactivity of the pituitary-adrenal system of adult rats with hereditary stress-induced arterial hypertension (HSIAH) [6].

EXPERIMENTAL METHOD

Experiments were carried out on rats of two genetic groups HSIAH (the 15th generation of selection, mean systolic pressure 183 ± 2.9 mm Hg) and Wistar (mean arterial pressure for the population 126 ± 3 mm Hg), from which the HSIAH rats were obtained by selection. Females were mated with males of the corresponding genetic groups and on the 16th-18th day after copulation (determined by the presence of spermatozoa in the vaginal smear) hydrocortisone (5 mg/100 g body weight) or 0.5 ml of physiological saline was injected subcutaneously into the animals, or they were left intact. The male progeny of these females were investigated at the age of 3-4 months. The males were put into individual cages one week before the experiment. Blood for fluorometric determination of 11-hydroxycorticosteroids (11-HCS) [9] was taken from the tip of the tail under superficial ether anesthesia, or from the trunk after decapitation [3]. The initial 11-HCS concentration was determined in blood taken immediately after removal of the rat from its cage. Emotional stress was induced by restricting the animal's movements for 1 h in a cylindrical constraining cage [3]. In combined stress, 1 ml of blood was taken from the tip of the animal's tail in the course of 2 min under superficial ether anesthesia, or after which the rat was kept in unfamiliar surroundings for 1 h. Through guide cannulas, inserted beforehand (4 days before the experiment) into the lateral ventricle of the rats, noradrenalin bitartrate (10 μg), carbachol (1.5 μg), or physiological saline, was injected in a volume of 10 μl. Blood was taken 1 h after the beginning of action of the stressors or of injection of the substances into the brain. Details of the method were described previously [3].

EXPERIMENTAL RESULTS

Adult rats whose mothers had received physiological saline or no treatment whatsoever during pregnancy were indistinguishable with respect to all features tested in both genetic

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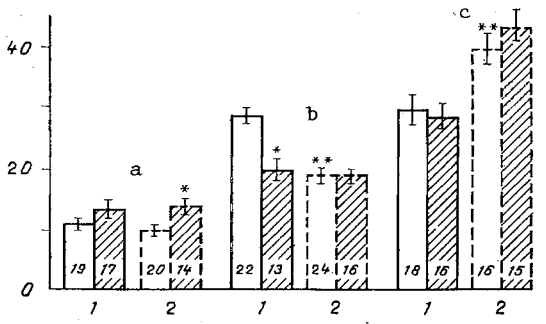

Fig. 1. Blood 11-HCS level (M ± m; in μg% of adult male Wistar (1) and HSIAH (2) rats in initial state (a) and during emotional (b) and combined (c) stress. Unshaded columns — control animals; shaded — after prenatal treatment with hydrocortisone. Numbers in columns indicate number of animals. * — Differences compared with animals of the same line, not treated with hormones, are significant; ** — compared with control Wistar rats.

lines. They were therefore amalgamated to form single control groups of rats of both Wistar and HSIAH lines.

The initial blood 11-HCS level of the control HSIAH and Wistar rats was about the same (Fig. 1a). During emotional stress the blood 11-HCS level of the control HSIAH rats was lower, whereas during combined stress it was higher than in the corresponding group of Wistar animals (Fig. 1a, b). These results are in agreement with data obtained on SHR rats [10, 11]. By comparison with WKY rats, from which the hypertensive SHR line was obtained, it was shown that the response of the latter to corticosteroids was enhanced by electrical stimulation [10] but depressed by immobilization of the animals [11].

The increased blood corticosteroid concentration of pregnant Wistar rats, as in the writers' previous investigations [2, 3, 7, 8], while not changing the blood 11-HCS level in the adult progeny in the initial state or during combined stress (Fig. 1a, c), considerably depressed the response of their adrenocortical system during emotional stress (Fig. 1b). Hormonal stimulation during the period of embryonic development of the HSIAH rats increased the initial blood 11-HCS concentration in the adult state compared with the control (Fig. 1a) but did not change the response of the system, not only during combined but also during emotional stress (Fig. 1b, c).

After injection of physiological saline into the lateral ventricle the blood 11-HCS concentration in rats of both groups was virtually the same and did not differ from its initial value (Fig. 2a). Control HSIAH rats had a lower 11-HCS concentration than the corresponding group of Wistar rats during stimulation by noradrenalin (Fig. 2b). This fall is in agreement with weakening of the function of the brain catecholaminergic mechanisms in hypertensive animals [5]. However, after injection of carbachol into the brain, there was no difference between the control rats of the two genetic groups (Fig. 2c).

Prenatal administration of hydrocortisone, just as in [7], depressed activation of the pituitary-adrenocortical system in adult Wistar rats as a result of injection of noradrenalin into the brain (Fig. 2b), but did not change the 11-HCS level during stimulation by carbachol (Fig. 2c). The direction of the modifying action of the hormone in the prenatal period of development on the noradrenalin mechanisms of the brain of adult HSIAH rats was opposite to that found in male Wistar rats (Fig. 2b). Whereas in Wistar rats the prenatal injection depressed the reactivity of the pituitary-adrenal system in response to injection of noradrenalin into the brain, in HSIAH it increased (compared with the corresponding control groups). Unlike in Wistar rats, injection of hydrocortisone into pregnant HSIAH rats lowered the blood 11-HCS level of their adult progenies in response to stimulation by carbachol (Fig. 2c).

Elevation of the glucocorticoid level during intrauterine development of HSIAH rats thus modifies their adrenocortical function. However, the character of the modifying action of the hormone on these rats differed considerably from that found in Wistar rats: in the lat-

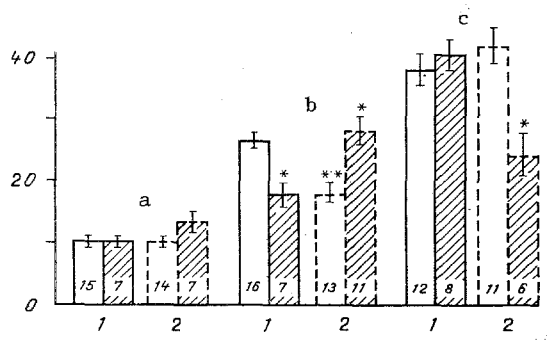

Fig. 2. Blood 11-HCS level (M ± m; in μg%) after injection of physiological saline (a), noradrenalin (b), or carbachol (c) into the brain. Legend as in Fig. 1.

ter prenatal exposure to hydrocortisone depressed the response of the pituitary-adrenocortical system to emotional stress and intracerebral injection of noradrenalin, whereas in HSIAH rats similar exposure raised the initial blood level of 11-HCS and increased the response of the system to stimulation by noradrenalin, but depressed the adrenocortical response to intraventricular injection of carbachol.

Incidentally, the modified level of sensitivity of HSIAH rats to noradrenalin corresponded to the control in male Wistar rats (Fig. 2b). In other words, prenatal exposure to hydrocortisone "corrected" the lowered sensitivity of the brain noradrenergic system induced by selection of the animals for high blood pressure. However, the increase in the sensitivity of HSIAH rats to noradrenalin took place without any change in the response to the emotiogenic stressor. Meanwhile in Wistar rats, as observed previously [2, 3, 7, 8], as a result of a change in the corticosteroid balance in the period of intrauterine development, a change in the sensitivity of the adrenocortical system to noradrenalin and in its reactivity to emotional stress developed. The disparity between these after-effects of hormonal exposure in HSIAH rats may be connected with the inhibitory effect of hydrocortisone on the cholinergic system of their brain [1]. The opposite character of the changes in these neurochemical mechanisms could facilitate preservation of their own characteristic level of response to emotional stress in HSIAH rats. It must also be pointed out that prenatal exposures did not lower the level of hypertension, which was 160-170 mm Hg in adult female HSIAH rats in all three series (intact animals, injections of hydrocortisone and of physiological saline).

The results indicate differences in the modifying action of glucocorticoids when injected before birth into normotensive and hypertensive rats on the formation of function of the adrenocortical system. These differences may be linked with the hereditary features of organization of the CNS and the formation of its function in HSIAH rats during development [5]. Elevation of the glucocorticoid level of hypertensive rats in the prenatal period of development "corrected" to some extent the hereditary deficiency of central noradrenergic regulation of the adrenocortical system.

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