Changed Activity of the Hypothalamic-Pituitary-Adrenocortical System in Prenatally Stressed Female Rat during Aging

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We studied the effects of daily 1-h immobilization of female rats on days 15-18 of pregnancy on functional activity of the hypothalamic-pituitary-adrenocortical system and its sensitivity to regulatory signals realized by the negative feedback mechanism in female progeny during aging. Prenatal stress potentiated the inhibitory processes in young animals. In aging female rats, the sensitivity of the hypothalamic-pituitary-adrenocortical system to feedback signals significantly decreased and circadian stress reactivity was disturbed. These data suggest that maternal stress modifies the age-related pattern of the hypothalamic-pituitary-adrenocortical regulation in female progeny.

Key Words: *prenatal stress; hypothalamic-pituitary-adrenocortical system; aging; rat*

Maternal stress, particularly during the last third of gestation, has a strong impact on the development of the progeny. Adult prenatally stressed rats demonstrated significant long-lasting disorders in the neuroendocrine regulation of reproduction, hormonal adaptation, and behavior depending on animal sex [2,4, 6,13]. Disorders in stress reactivity and sensitivity of all components of the hypothalamic-pituitary-adrenocortical system (HPAS) to regulatory signals in young animals were described [2,7,10,14].

According to the neuroendocrine theory of aging, which received numerous experimental validations in recent years, this process is paralleled by reduction of the efficiency of the feedback contour between the hypothalamus and other endocrine glands [1,11]. The modifying effect of maternal stress on age-specific stress reactivity and HPAS regulation processes in prenatally stressed individuals attracts special interest, because changed pattern of functioning of the system is a component of complex disorders leading to psychophysiological abnormalities. We studied the impact of stress exposure of pregnant females during the last third of gestation for functional activity of HPAS and its sensitivity to the regulatory signals in female progeny during aging.

MATERIALS AND METHODS

Female progeny of 10 primiparous Wistar rats was examined. The animals were kept under standard vivarium conditions with free access to water and food. Pregnant females (n=5) were daily (on days 15-18 of gestation) exposed to immobilization stress in narrow plastic boxes 20×7×6 cm under conditions of bright illumination. Control pregnant females (n=5) were left intact. The pups were kept with mothers until the age of 30 days, after which they were kept 6 per cage.

The processes of HPAS inhibition by the negative feedback mechanism were studied in 3-, 12-, 18, and 24-month-old experimental and control females (8 per group) using 2-day dexamethasone test [3]. Dexamethasone was injected intraperitoneally in a dose of 5 μg/kg.

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The dynamics of hormonal stress reaction in response to 20-min immobilization was studied in 11-month-old females (10 per group) by the method described previously [2].

Circadian dynamics of HPAS activity was studied in 13-month-old prenatally stressed (n=18) and control (n=16) females according to a previously described protocol [3].

Plasma corticosterone concentration was measured by radioimmunoassay using antisera prepared in our laboratory and [1,2,6,7-^{3}H]-corticosterone with specific activity of 76.5 Ci/mmol (NEM™, Life Science Products).

The results were processed using Student's t test. The differences were significant at $p<0.05$.

RESULTS

In control females the basal and stress-induced plasma corticosterone concentration decreased at the age of 12 and 18 months, respectively, compared to young (3-month-old) animals (Table 1). Study of HPAS inhibition processes showed that the sensitivity of the system to feedback signals in females aged 1 year remained at the level typical of young animals, while later the exogenous hormone reducing corticosterone level at rest did not prevent the adrenocortical reaction to stress. Hence, aging in control females was associated with impairment of inhibition mechanisms in HPAS regulation.

Basal and stress-induced levels of corticosterone in female progeny of stressed mothers did not differ from those in control animals at all stages of the study. Similar results were obtained in a previous study [4], which also revealed no changes in the level of adrenocortical stress-reaction in 20-22-month-old females with a history of prenatal stress. Study of HPAS regulation by the negative feedback mechanism showed that dexamethasone injection led to a more pronounced inhibition of HPAS activity in young 3-month-old experimental females in comparison with control animals. However, the level of corticosterone in 1-year-old experimental females against the background of exogenous hormone was higher, which reflects reduction of HPAS inhibition by the feedback signals. Similar pattern of HPAS activity regulation was retained in 18-month-old prenatally stressed rats. Experimental females exhibited higher sensitivity of HPAS to feedback signals in comparison with control rats, which manifested in reduction of not only basal, but also stress-induced level of corticosterone after injection of dexamethasone. Further study showed that regulation of functional activity of HPAS by the negative feedback mechanism in old (24-month-old) pre-

TABLE 1. Dexamethasone Test in Female Wistar Rats of Different Age with a History of Prenatal Stress (nmol/liter; $M\pm m$)

Age, months	Control				Prenatal stress			
	saline		dexamethasone		saline		dexamethasone	
	basal level	stress level	basal level	stress level	basal level	stress level	basal level	stress level
3	437.71±87.97	1322.74±120.43	148.17±31.45*	260.78±37.24*	444.44±66.88	1183.93±84.70	89.48±18.64*+	153.80±17.76*+
12	291.900±56.002	1113.06±86.66	59.98±22.72*	230.06±80.17*	338.49±88.57	913.21±52.48	104.72±46.63*	570.40±108.99*+
18	205.94±28.902	415.58±62.88	97.14±17.98*	407.13±24.84	204.91±21.67	476.19±43.78	117.01±23.03*	265.93±30.34*+
24	254.68±21.66	803.29±90.63	118.16±24.53*	914.15±64.66	205.28±21.59	745.70±37.74	268.42±38.81+	1094.28±130.96

Note. $p<0.05$ compared to *injection of saline, +control.

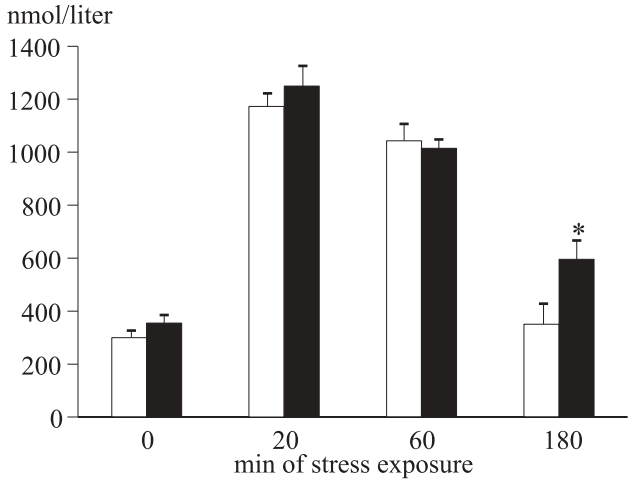

Fig. 1. Effect of prenatal stress on the dynamics of corticosterone secretion in response to 20-min immobilization in 11-month-old female rats. Here and in Fig. 2: light bars: control group; dark bars: experimental group. Ordinate: plasma corticosterone content. *$p<0.05$ compared to the control.

natally stressed female rats was significantly disturbed, because dexamethasone injection did not change corticosterone concentrations at rest and during stress. Hence, maternal stress modified the regulation of HPAS in female progeny, stimulating inhibition processes in young rats and reducing the sensitivity of the system to feedback signals during aging.

This conclusion was confirmed in studies of the dynamics of hormonal stress reaction in 1-year-old females with a history of prenatal stress (Fig. 1). Blood corticosterone concentration in experimental animals 180 min after the start of stress exposure significantly surpassed the control level and hence, stress activation was not followed by HPAS inhibition. We previously showed that maternal stress is inessential for the stress response switch-off in 3-month-old female descendants [2]; however, our new findings indicate that the efficiency of negative feedback mechanisms in HPAS regulation decreases with age in these animals.

Our results are in good agreement with the neuroendocrine concept of aging, attributing this process to reduction of the efficiency of the hypothalamus-pituitary feedback contour [1]. It was also shown that uneven stimulation of individual hypothalamic nuclei of stray directions emerged in old rats exposed to stress [5]. The effect of prenatal stress on changes in HPAS regulation by the feedback mechanism can be due to a weaker inhibitory effect of the extrahypothalamic regulation contour on HPAS. It is known that maternal stress not only impairs the hippocampal neurogenesis, but leads to reduction of the glucocorticoid receptor binding activity in this structure [7,8,12] and in the frontal cortex and amygdala [10] of adult animals. Moreover, reduced sensitivity of brain structures to glucocorticoid hormones can be mediated by the prenatal stress effects on the content and turn-over of some neuromediators. It was shown that prenatal stress modified activities of the cerebral noradrenergic and serotoninergic systems not only in young, but also in old rats [4,8].

Circadian rhythm of corticosteroid secretion is, no doubt, an indicator of functional activity of HPAS. We studied circadian dynamics of hormonal secretion in female rats aged 13 months. It was found that circadian activity of HPAS in control females was intact and during the morning hours the animals had minimum basal levels of corticosterone and exhibited maximum stress reactivity (Fig. 2). Basal hormone level in females born from mothers exposed to stress at the end of gestation did not differ from that in controls throughout 24 h. A significant reduction of stress concentration of cor-

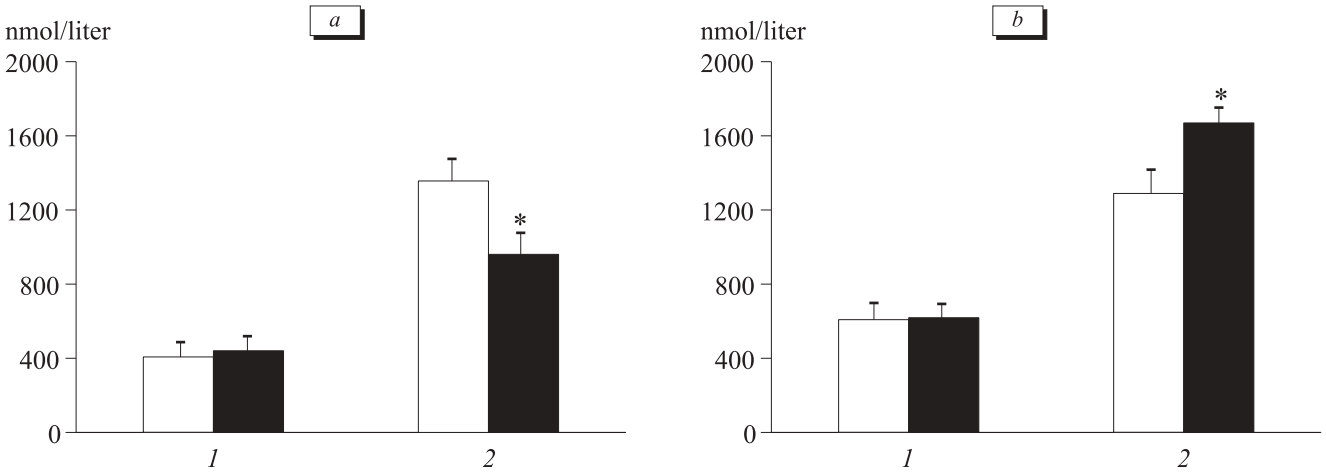

Fig. 2. Effect of prenatal stress on circadian dynamics of corticosterone secretion in 13-month-old female rats. *a*) morning (9:00); *b*) evening (21:00). *1*) basal corticosterone level; *2*) stress-induced corticosterone level.

ticosterone in the blood was recorded during the morning hours. At 21:00 prenatally stressed females exhibited higher stress reactivity in comparison with control animals. Analysis of the results showed that at 9:00 experimental females were characterized by a significantly lesser mean increment in corticosterone concentration in response to stress exposure in comparison with control animals (614.10±109.12 and 949.20±97.85 nmol/liter, respectively; p=0.04), though in the evening hours the increment of corticosterone level did not reach the level of significance (1119.50±34.86 and 1033.50±99.66 nmol/liter, respectively). Disorders in the circadian rhythms of all HPAS components in young prenatally stressed rats of both sexes were detected in other studies [9]. For example, high level of corticosteroid secretion at the end of the light hours of the day and high hypercorticism over 24 h were detected in adult females.

Hence, maternal stress significantly modified the age-related pattern of HPAS regulation in female progeny. Disorders of circadian stress reactivity and significant reduction of the efficiency of HPAS feedback contour were detected in aging females with a history of prenatal stress.

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