SEX DIFFERENCES IN ADRENOCORTICAL SENSITIVITY AND RESISTANCE TO CEREBROVASCULAR LESIONS IN RATS EXPOSED TO SEVERE STRESS

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The sharp increase in stress overloads in the life of modern man has revealed weakened powers of adaptation in men than in women, as is shown by the greater tendency of men to develop hypertension, ischemic heart disease, myocardial infarction, stroke, and peptic ulcer [5, 9, 14]. The study of individual differences in stress and adaptation has shown strong correlation between the functional reserves of steroid production and the stress-resistance of the various systems. The amplitude of the glucocorticoid response to stress and to ACTH correlates positively with the functional reserves of the cardiovascular system [3, 4, 12], and with resistance to ulcer formation [11].

It can be tentatively suggested that not only individual, but also sex differences in powers of adaptation are largely determined by the pattern of sexual dimorphism of sensitivity of the hypothalamo–hypophyseo–adrenocortical system to stress. The aim of this investigation was to test this hypothesis, by studying the dynamics of the adrenocortical response and resistance to cerebrovascular lesions in female and male albino rats exposed to severe stress.

EXPERIMENTAL METHOD

Acoustic stress for 2 h against a background of strict immobilization [8] was used as the extremal stimulus, leading to cerebral hemorrhage. Adrenocortical sensitivity was estimated on the basis of changes in the corticosterone concentration, determined fluorometrically, in the adrenals and blood plasma 10, 60, and 120 min after the beginning of stress and 1, 2, 4, and 24 h after its end. The brain was taken from animals decapitated immediately and also 1 and 24 h after the end of stress, and fixed in 10% formalin solution. Dewaxed sections were stained with hematoxylin and eosin, with Heidenhain's iron-hematoxylin, and by Mallory's and Nissl's methods. To assess the state of the blood flow in the microcirculatory bed of the thalamic region the number of functioning capillaries in 10 fields of vision of the microscope was counted, and the diameter of the arterioles was measured in the region of the thalamus and brain stem. Disturbances of vascular permeability were judged from the number of hemorrhages in a sagittal section through the hemispheres. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The corticosterone concentration in the adrenals of the female rats rose by 3.6 times 10 min after the beginning of stress and remained virtually unchanged until the end of stress (Fig. 1a). The plasma level of the hormone after 10 and 60 min was 4.6 and 4.1 times higher than the basal values, and by the end of stress it was 6.6 times higher. The corticosterone concentration in the adrenals of the males increased by 2.6 times after exposure

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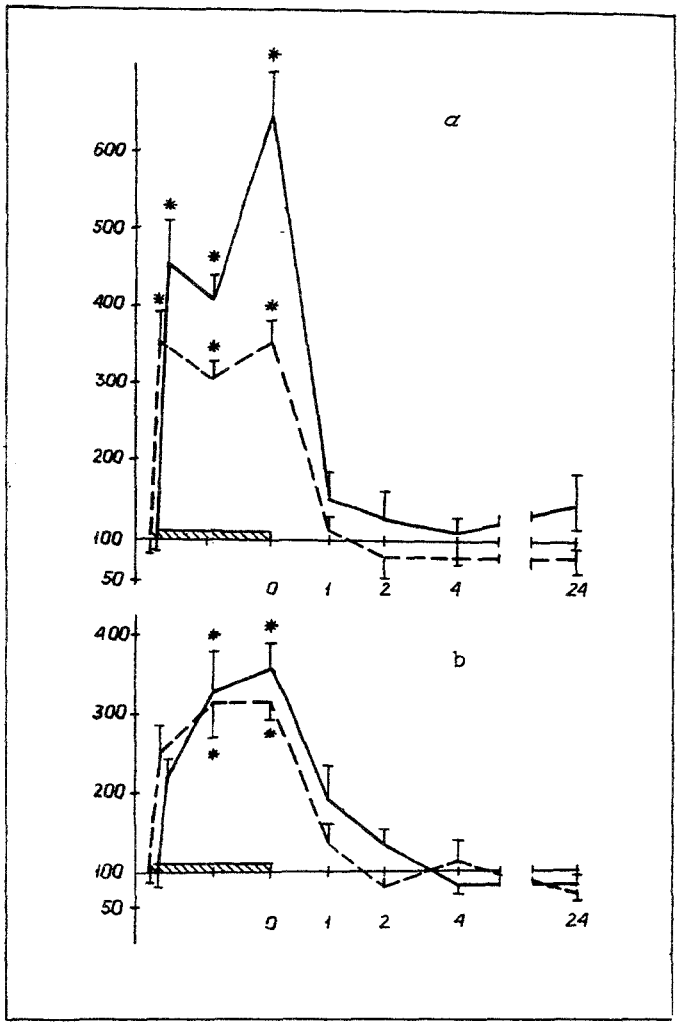

Fig. 1. Dynamics of changes in corticosterone concentration in females (a) and males (b) during exposure to severe stress. Abscissa, time (in h); ordinate, corticosterone concentration (in percent of control) in adrenals (broken line) and blood plasma (continuous line). *) Change significant compared with control ($p < 0.05$). Each point represents $M \pm m$ for 6-12 animals.

to stress for 10 min, and remained at about the same level until its end (Fig. 1b). The hormone concentration in the plasma after 10 and 60 min was increased by 2.2 and 3.3 times, and did not increase further before the end of stress. Consequently, throughout the period of action of the stress factor, especially in the initial and final stages, the plasma corticosterone level of females was significantly higher than that of males ($p < 0.001$). It is remarkable that in females the amplitude of the adrenocortical response was more than twice as high as in males even during the first 10 min. The increased adrenocortical sensitivity of the females in this case was combined with ability to increase the intensity of steroid production in the second hour of stress, which was not observed in males. This indicates higher functional reserves of steroid production in females. The corticosterone concentration in the adrenals and plasma 60 min after the end of stress did not differ from the basal levels in the majority of females and males, but after 2 h

TABLE 1. Sex Differences in Development of Cerebrovascular Disturbances Induced by Stress

Series of experiments	Number of animals	Sex of rats	Number of functioning capillaries	Number of perivascular hemorrhages per section			
				arterioles	venules	capillaries	total number
Control	7	Females	10,1±0,3	—	—	—	—
	10	Males	9,6±0,5	—	—	—	—
Stress Immediately	8	Females	7,8±0,5*	2,2±0,2	1,8±0,3	2,7±0,2	6,7±0,2
	10	Males	8,2±0,7	2,5±0,1	2,9±0,3▲	3,1±0,4	8,5±0,3▲
After 1 h	9	Females	12,2±0,6*	2,8±0,6	2,0±0,4	5,3±0,4●	10,1±0,5●
	10	Males	13,9±0,8*	4,8±0,5●▲	5,2±0,6●▲	7,4±0,5●▲	17,4±0,5●▲
After 24 h	8	Females	8,8±0,6	3,1±0,6	2,3±0,2	8,2±0,7●	13,6±0,5●
	10	Males	11,5±0,4*▲	5,1±0,4▲	6,3±0,3▲	11,4±0,9●▲	22,8±0,6●▲

Legend. Change is significant ($0.001 < p < 0.05$) compared with control (asterisk), previous level (black circle), and between females and males (triangle).

the hormone levels returned to normal in all females and males and remained within normal limits 4 and 24 h later. Consequently, just as during exposure to physiological stressors [1, 2], in severe stress the intensity of steroid production was significantly higher in females than in males.

These results were compared with the resistance of females and males to stress-induced cerebrovascular lesions (Table 1). The pathogenic effect of stress on the cerebral hemodynamics was discovered immediately after its end and expressed as moderate hyperemia of the brain due to vasodilatation. The latter was accompanied by increased vascular permeability for erythrocytes and plasma proteins, evidence of disturbances of self-regulation of the cerebral blood flow [6, 13, 15]. In females, however, these disturbances were less marked. Development of small focal hemorrhages as a result of disturbance of vascular permeability was observed in 100% of the males but only in 62% of the females. The number of hemorrhages near the venules was less in females than in males. It will be noted that the number of functioning capillaries was increased in the females but not in the males.

Moderate hyperemia with signs of stasis of erythrocytes in the dilated vessels still remained 1 h after the end of stress in the brain of all the males and 78% of the females. Intensification of cerebral hypoxia was shown by the appearance of numerous nerve cells with hyperchromic nuclei in the region of the reticular nucleus of the thalamus and nuclei of the medulla. Congestive features in the capillary network were more marked in males. For instance, the number of capillaries in the brain tissue was 44.8% greater than the control in the males, but only by 20.7% in the females. In males 28% of the arterioles in a section through the brain stem were in a state of dilatation, but only 15% in females. The process of disturbance of vascular permeability progressed further in males than in females. In the course of an hour the number of small focal hemorrhages around arterioles, venules, and capillaries increased in the males, but only around the capillaries in females. As a result the total number of perivascular hemorrhages in the males was 1.7 times higher than in the females.

After 24 h moderate cerebral hyperemia still remained in all parts of the microcirculatory bed. The total number of perivascular hemorrhages was increased mainly due to the capillary portion, and remained 1.7 times higher in the males than in the females. Meanwhile in females the density of the capillary network at this time did not differ from that in the control, reflecting normalization of the cerebral blood flow. In males, however, signs of congestion in the capillary network of the brain remained the same as in the first hour after exposure to stress. Absence of normalization of the blood supply of the brain and preservation of hypoxia in the males indicated an increase in the number of ischemically changed nerve cells in the reticular nucleus and in the ventrolateral portion of the thalamus of the males.

Consequently, stress-induced cerebral hyperemia and disturbances of vascular permeability, leading to the development of small focal hemorrhages were less marked in females than in males at all stages of the investigation. Individuals resistant to changes in the cerebral hemodynamics in this type of stress were found among the females,

but not among males. The results, together with the evidence of increased resistance of females to experimental myocardial infarction [7, 10], point to a greater degree of protection of females against cardiovascular disturbances induced by exposure to stress. The ability to reproduce in animals sex differences in resistance to cardiovascular pathology, that are typical of man, is evidence that the mechanisms of this phenomenon are the same in man and animals. Positive correlation between hormonal stress-reactivity and stress-resistance of the cerebral hemodynamics suggests that the higher resistance of females to stress-induced cardiovascular pathology is largely due to the high adrenocortical sensitivity and increased functional reserves of steroid production.

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