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ANALYSIS OF FACTORS DETERMINING SEX DIFFERENCES IN RESPONSES OF ALBINO RATS TO STRESS

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UDC 613.863-055.1/2-07

KEY WORDS: stress; sex differences; infants; castrates; neonatal androgenization

Sex differences in the sensitivity of rats to physiological stressors, discovered by the writers previously [1], are in good agreement with observed sex differences in resistance to particular types of pathology, arising in clinical practice [8] and experimentally [10]. Elucidation of the factors determining these differences depends primarily on a study of the role of sex hormones, for their level determines sex differences in a number of morphological structures [12, 15] and biochemical parameters [5, 6, 14], involved in adaptive processes.

The aim of these investigations was to study stress-induced reactions in infantile and adult intact and castrated female and male albino rats, and also in adult, neonatally androgenized females.

EXPERIMENTAL METHOD

Activity of stress-realizing mechanisms was investigated in females and males in situations of emotional and emotional-painful stress, not going beyond the limits of physiological stress factors either qualitatively or quantitatively. Emotional stress (ES) was induced by the sight and the cries of bound partners, and emotional-painful stress (EPS) by immobilization for 10 min. The intensity of the stress response was assessed on the basis of changes in the corticosterone concentration in the adrenals and blood plasma, determined fluorometrically. Responses to stress were studied in immature rats (weighing 70-100 g), in adult intact rats and rats castrated 3 weeks before the experiment, and in adult females receiving a subcutaneous injection of 1 mg of testosterone propionate at the age of 1 day. Altogether 362 rats were used.

Departments of Biochemistry, Biophysics, and Physiology, N. G. Chernyshevskii, Saratov University. (Presented by Academician of the Academy of Medical Sciences of the USSR K. S. Sudakov.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 108, No. 11, pp. 616-618, November, 1989. Original article submitted March 9, 1989.

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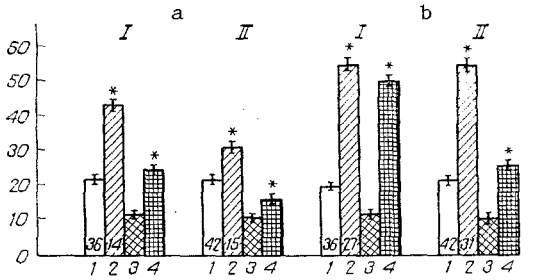

Fig. 1. Response of intact rats to ES (a) and EPS (b). Ordinate, corticosterone concentration (in adrenals in μg/g; in blood plasma in μg %). 1, 2) Corticosterone in adrenals (1 – control, 2 – stress), 3, 4) corticosterone in plasma (3 – control, 4 – stress). Numbers at foot of column denote number of animals in groups. I) Females, II) males. *) Significant differences ($p < 0.05$-0.001).

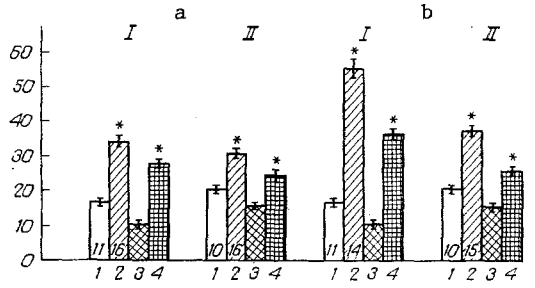

Fig. 2. Response of castrated rats to ES (a) and EPS (b). Legend as to Fig. 1.

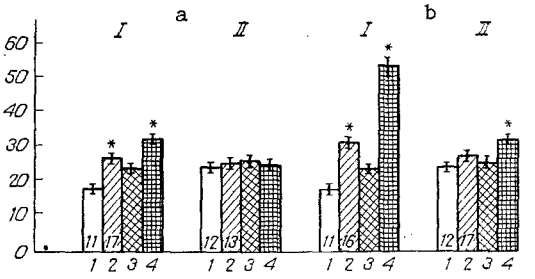

Fig. 3. Response of immature rats to ES (a) and EPS (b). Legend as to Fig. 1.

EXPERIMENTAL RESULTS

Adult rats exhibited sex differences in activity of their stress-realizing mechanisms during ES and EPS. For instance, in response to the sight and cries of their bound partner, the corticosterone concentration in the adrenals and blood plasma of the female rats was doubled, whereas in males it was increased by only 1.4 times (Fig. 1a). Female rats in a situation of ES were mobile, and exhibited clear emotional resonance relative to their bound partners, whereas the characteristic response of the males was passive-defensive, of the immobility type. During EPS, sex differences were clearly visible in the intensity of secretion of corticosterone, the plasma level of which rose fourfold in the female rats but by only 2.3 times in males (Fig. 1b).

Castrated animals preserved their sex differences in sensitivity to unfavorable influences. In females ES was accompanied by elevation of the corticosterone level in the adrenals and plasma by 2 and 2.5 times. In males, synthesis and secretion of the hormone were increased by 1.4 and 1.6 times (Fig. 2a). In response to stronger EPS the response of the castrated females took the form of a 3.3-fold increase in the synthesis and secretion of corticosterone. In castrated males, the concentration of the hormone in the adrenals and plasma rose by only 1.8 and 1.6 times (Fig. 2b). Incidentally, castration of both females and males led to some decrease in corticosterone secretion in response to EPS, possible evidence of the modulating effect of both male and female sex hormones on the intensity of the response to stress. Meanwhile the maintenance of sex differences in the activity of stress-realizing mechanisms in castrated animals indicates that these differences are independent, in principle, of sex hormones.

In connection with the facts discovered it is interesting to elucidate the character of stress responses in immature animals. During ES, corticosterone synthesis and secretion by infantile females increased by 1.5 and 1.4 times. In infantile males there was no increase in the corticosterone concentration in either adrenals or blood plasma, indicating that they are refractory to ES (Fig. 3a). During EPS, synthesis and secretion of the hormone by infantile females increased by 1.7 and 2.3 times, whereas in males, only secretion of corticos-

terone rose by 1.3 times, and its concentration in the adrenals was unchanged (Fig. 3b). Thus in infantile animals compared with adults, the intensity of stress reactions is significantly lower, evidence of the depressed powers of adaptation in early ontogeny. Meanwhile in females, the adaptive mechanisms at this age can already maintain an adequate response to unfavorable influences, whereas in infantile males, the stress realizing mechanisms are less well developed at this age. Comparison of stress reactions in infantile and adult animals illustrates P. K. Anokhin's well-known hypothesis that functional systems responsible for adequate reactions to external, in this case stress, stimuli, are formed in ontogeny in accordance with the principle of minimal provision for functions [2]. The extremely weak sensitivity of infantile males compared with females, exhibited in these experiments, is evidence of sex differences in the ontogenetic maturation of adaptive systems. A clinical illustration of the advantage of earlier maturation in ontogeny of adaptive systems is given by the results of 6-year observations on a risk group of neonates, which revealed greater susceptibility of boys to diseases than of girls [13].

The independence of sex differences in sensitivity to stress of sex hormones, discovered in these experiments, does not in principle rule out the possibility that these differences may be determined by processes of sexual differentiation of the brain. To test this hypothesis, we studied the response of adult neonatally androgenized females to immobilization. In these animals neonatal androgenization, inducing an anovulatory syndrome with failure of the vagina to open [9], did not abolish the sexual dimorphism typical of intact animals in the weight of the adrenals: in intact females and males it was 24 and 16 mg/100 g respectively, compared with 28 mg/100 g in androgenized females. The stress reaction in females with masculinized brain followed the female type of course. During EPS, for instance, the corticosterone concentration in the adrenals and blood plasma rose by 3.1 and 3.9 times (by 2.5 and 4 times in noncastrated females). These data are evidence that sex differences in stress reactions are unconnected with processes of sexual differentiation of the brain.

The sex differences found in sensitivity to physiological stressors are thus characteristic only of adult animals and not of infantile or castrated animals, and they are not modified by masculinization of the brain in females. Consequently, they are genetically determined.

Our conclusions on the genetic origin of sex differences in stress reactions make a serious further contribution to the concept of genetic determination of individual [3] and interlinear [4, 7, 11] differences in resistance to stress, undergoing development at the present time.

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