SEX DIFFERENCES IN SENSITIVITY OF ALBINO RATS TO ADRENALIN

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KEY WORDS: sex differences; corticosterone; stress; adrenalin

Our previous investigations showed that the amplitude of the adrenal cortical response of female albino rats is almost twice that observed in males, throughout the period of exposure to stress, irrespective of its intensity and duration [1, 2]. These differences can be largely ascribed to the higher activity of the mediator and hormonal divisions of the sympathoadrenal system in females than in males. This possibility is based on the fact that basal levels of catecholamines in the brain [15] and basal and stressor levels of catecholamines in the heart and adrenals [11] are higher in females. Meanwhile, the efficiency of function of the sympathoadrenal system is determined not only by the level of production of catecholamines, but also by the sensitivity of hypothalamic structures to them. In this connection we decided to study sex differences in sensitivity to adrenalin, which plays an important role in the physiological mechanisms of stress [6].

The aim of the investigation was to study the time course of changes in the intensity of steroid production in female and male albino rats receiving injections of adrenalin.

EXPERIMENTAL METHOD

Experiments were carried out on 200 adult noninbred female and male albino rats. The animals were kept four to a cage for 5 days before the experiment began to bring about social adaptation. Adrenalin was injected intraperitoneally in a dose of 20 μg/100 g. The control animals received a similar injection of physiological saline. Concentrations of corticosterone in the adrenals and blood plasma, collected after decapitation of the animals 10, 30, 60, 120, 180, and 240 min respectively after the injection, were determined fluorometrically. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

Sensitivity to adrenalin involves a nonspecific component, associated with the injection procedure, and a specific component, due to the stimulating action of adrenalin on the hypothalamo-hypophyseo-adrenal system. Since sympathomimetic models of stress are not accompanied by activation of the nervous apparatus of the emotions and, consequently, of the sympathoadrenal system [9], reactions to injected adrenalin involved virtually no participation of endogenous catecholamines.

The concentrations of corticosterone in the adrenals and plasma of female rats 10 min after injection of physiological saline were increased by 3.0 and 3.2 times respectively (Fig. 1). However, by the 30th minute the normal hormone level was restored. Slight fluctuations in the corticosterone concentration at later times of observation reflect the fluctuating character of the recovery processes [8].

The response of males to injection of physiological saline was weaker in amplitude than in females, and recovery was slow. The concentration of the hormone in the adrenals and plasma 10 min after injection of the solution was increased by only 1.9 and 1.7 times, but remained at the same level until the 30th minute (Fig. 2). Later

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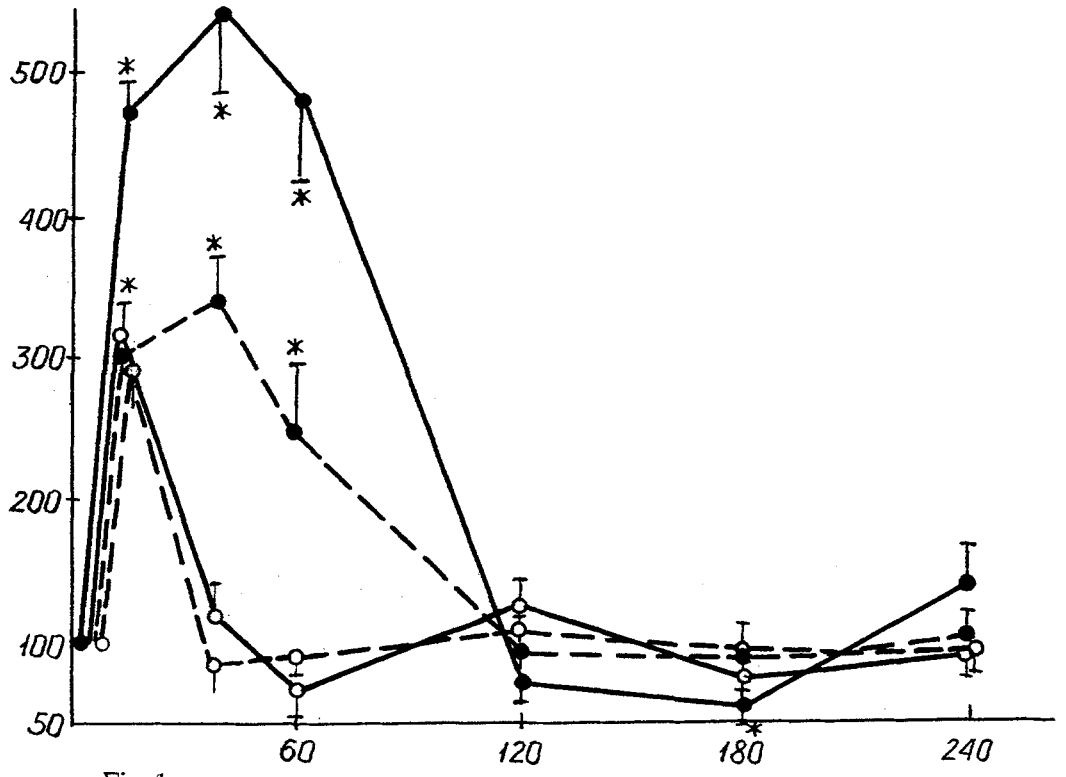

Fig. 1

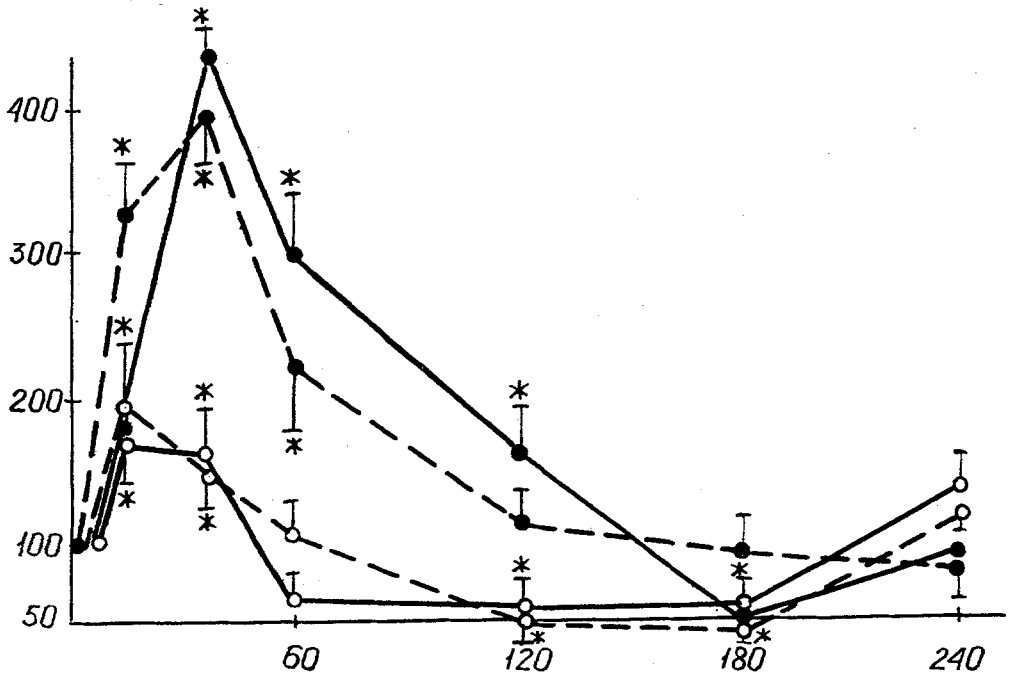

Fig. 2

Fig. 1. Dynamics of corticosterone concentration in adrenals (broken line) and plasma (continuous line) of female rats receiving injections of physiological saline (empty circles) and adrenalin (filled circles). Abscissa, time (in min); ordinate, corticosterone concentration (percentage of basal level). Asterisk indicates significant shift compared with basal level ($p < 0.05$-0.001). Each point represents $M \pm m$ for 7-12 animals.

Fig. 2. Time course of corticosterone concentration in adrenals (broken line) and blood plasma (continuous line) of male rats receiving injections of physiological saline (empty circles) and adrenalin (filled circles). Legend as to Fig. 1.

in the males, by contrast with the females, depression of steroid production was observed, as shown by a 50% fall of the corticosterone levels 120-180 min after injection. Normal values were not restored until the 240th minute.

The specific effects of adrenalin was exhibited as early as 10 min after its injection. Since extrinsic adrenalin requires at least 30 min to pass through the blood–brain barrier [5], this rapid action of adrenalin evidently reflects the reflex pathway of excitation of ACTH secretion, studied in rats, in response to hypotension induced by adrenalin through β-adrenoreceptors [10]. In females the plasma corticosterone level rose under these circumstances by 4.6 times, equivalent to 146.5% of the plasma corticosterone level of the control rats (Fig. 1). The absence of any decrease in the corticosterone concentration in the adrenals of the female rats receiving adrenalin, compared with the control rats, is evidence of potentiation not only of secretion, but also of synthesis of the hormone by adrenalin.

In males the specific effect of adrenalin after 10 min was limited to an increase in corticosterone synthesis in the adrenals, where its level was 1.6 times higher than that of the control animals (Fig. 2). Consequently, in the first 10 min of action of adrenalin the degree of enhancement of steroid production was higher in females than males, possibly due to the greater working efficiency of the corresponding reflex mechanisms in females.

Potentiation of the stimulating effect of adrenalin during the subsequent times of observation, reflecting the central mechanism of its action, was accompanied by an increase in sex differences in sensitivity to adrenalin. In females, the specific effect of adrenalin was manifested to the full 30 min after its injection, when the reaction to the injection procedure had ended. By this time the corticosterone concentration in the adrenals and plasma was increased by 3.4 and 5.5 times respectively compared with the basal level (Fig. 1). In males the corticosterone concentration in the adrenals and blood plasma at the 30th minute was 3.9 and 4.3 times higher than the basal level (Fig. 2). However, the "true" reaction of the males to adrenalin at this time, allowing for the nonspecific reaction to the injection, which was still preserved, was little more than half of that of the females. By the 60th minute, when the response to the injection procedure had ended in both females and males, the plasma corticosterone concentration was increased by 4.8 times in the females, but by only 2.9 times in the males. In both females and males, by the 60th minute the corticosterone concentration in the adrenals was significantly lower than its previous value, reflecting weakening of the effect of adrenalin toward this time of observation. Later, the recovery period was characterized by faster normalization of the plasma corticosterone level in the females. In fact, whereas in females this parameter by the 120th minute did not differ from the basal values, in males it remained high. In both females and males, in the recovery period toward the 180th minute a phase of depression of steroid production was observed, followed by its normalization toward the 240th minute of observation.

Thus the response of the females to adrenalin was significantly higher, not only in the first phase of its reflex action, but also in the later period of its central action. The absence of any sex-linked differences in the basal levels of corticotrophin and its sensitivity to corticotrophin releasing factor [14], the basal level of corticosterone [1, 2, 12], and metabolic clearance of glucocorticoids [13] suggests that the more rapid activation of steroid production in females under the influence of adrenalin is determined by increased sensitivity of the hypothalamic structures of females to it. In our view, the enhanced reactivity of the hypothalamus to adrenalin in females makes an essential contribution to their higher amplitude of the glucocorticoid response compared with males, at the stage of excitation of both mediator and hormonal divisions of the sympathoadrenal system.

The search for factors determining sex differences in glucocorticoid sensitivity to stress cannot be confined to the boundary of the neuroendocrine system. An important role in this phenomenon may be played by sex differences in cardiohemodynamic shifts. Considering the inhibitory effect of hypertensin on the amplitude of the adrenocortical response [7] it can be tentatively suggested that the depressed adrenocortical sensitivity of males to stress, compared with females, is to a large extent due to their higher basal and stress-dependent levels of systolic blood pressure [3, 4, 16].

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THE USE OF THERMO- AND ACID-STABLE PROTEINASE INHIBITOR TO DEPRESS PROTEOLYSIS ACTIVATION DURING INFLAMMATION OF THE LUNGS

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The development of an imbalance in the proteinase–inhibitor system is an important pathogenetic factor in the development of inflammatory diseases of the lungs [1, 5, 13]. For this reason an intensive search is in progress, aimed at developing methods of treatment of lung diseases with the use of various preparations of proteinase inhibitors [10, 12, 14]. Among the most effective inhibitors are acid-stable proteins [7], one typical representative of whom is the thermostable and acid-stable inhibitor from rabbit blood serum (TASPI). This inhibitor is a close structural homolog of the acid-stable inhibitors from human blood plasma and urine [8], and its ability to inhibit cellular cathepsin D, elastase, kininogenase, and other proteinases of granulocytes has been described in detail [4, 6]. Special interest has been shown in this class of proteins in connection with the possibility of their clinical use [9].

The aim of this investigation was to compare the efficacy of TASPI, obtained from rabbit serum, as an inhibitor of activation of proteolysis during initiation of inflammation in the lungs with that of the trypsin inhibitor contrykal.

EXPERIMENTAL METHOD

Experiments were carried out on 65 Wistar rats weighing 200 g. Inflammation was initiated by introducing a capron thread 0.25 mm in diameter and 2.5-3 cm long into the animals' trachea. The animals were divided into the following groups: 1) control (healthy animals, n = 21); 2) rats developing inflammation for 24 h (n = 12); 3) rats receiving contrykal before fixation of the thread in the trachea and investigated 24 h later (n = 6); 4) similar to group 3, but receiving TASPI instead of contrykal (n = 6); 5) rats developing inflammation for 48 h (n = 8); 6) rats receiving contrykal 24 h after initiation of inflammation and studied 48 h later (n = 6); and 7) a group similar to

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