Stress-Limiting Effect of Dehydroepiandrosterone Sulfate and Its Mechanism

T. A. Obut, M. V. Ovsyukova, and O. P. Cherkasova

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Dehydroepiandrosterone sulfate prevented the increase in corticosterone level in rats induced by repeated exposure to stress. The μ-opioid receptor blocker naltrexone administered in a dose of 0.1 mg/kg 20 min before treatment with dehydroepiandrosterone sulfate abolished the effect of this agent. Dehydroepiandrosterone sulfate and naltrexone had no effect on rats after acute stress.

Key Words: *dehydroepiandrosterone sulfate; stress reactivity; μ-opioid receptors*

Androgens dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are synthesized not only in the zona reticulata of the adrenal glands [14], but also in the central nervous system (neurosteroids) [6,14]. Our previous studies showed that DHEA and DHEAS are involved in adaptive reactions and improve organism's resistance to stress-induced pathologies [2-4]. We found that synthetic DHEA analogue retabolil reduces stress reactivity in male rats during chronic stress [2]. However, the direct effect of DHEAS on stress reactivity and biological mechanisms underlying this influence remain unclear. It was hypothesized that the action of DHEAS is realized via the opioid mechanism [2]. The opioid system regulates activity of the hypothalamic-pituitary-adrenocortical system (HPACS) [1,5,8-10]. Published data show that opioid receptors mediate inhibition of stress-induced changes in HPACS [1,7]. However, it remains unclear whether the influence of DHEAS on stress reactivity is realized via opioid structures. Here we studied the effect of DHEAS on stress reactivity during acute and chronic stress and evaluated the role of μ-opioid receptors in DHEA-induced changes.

MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 160 g. The rats were subjected to single (1 h) or repeated (1 h per day, 19 days) shaking on an AVB-4p laboratory shaker (180 shakes per 1 min). Plasma corticosterone was measured by high-performance liquid chromatography. This parameter reflected stress reactivity of animals. DHEAS was injected in a dose of 30 mg/kg 2 days before decapitation. The μ-opioid receptor blocker naltrexone was administered in a dose of 0.1 mg/kg 20 min before treatment with DHEAS [7].

The results were analyzed by Student's *t* test. The differences were significant at $p<0.05$.

RESULTS

Single and repeated (19 days) stress exposure increased corticosterone level in male rats ($p<0.001$, Fig. 1). Corticosterone concentration after chronic stress was lower than after acute stress ($p<0.01$). Therefore, the stress-induced increase in corticosterone level was less pronounced after chronic stress. These data indicate that the reaction of HPACS is diminished after repeated stress. Our previous studies show that the decrease in stress reactivity of males is not related to exhaustion of the adrenal glands or HPACS [2].

The increase in corticosterone level induced by repeated stress was less pronounced in male rats receiving DHEAS ($p<0.05$). The mean concentration of corticosterone in repeatedly stressed rats receiving DHEAS practically did not differ from that in intact animals ($p>0.05$). After acute stress corticosterone level did not differ in rats receiving and not receiving

Institute of Physiology, Siberian Division of the Russian Academy of Medical Sciences, Novosibirsk. ***Address for correspondence:*** T.A.Obut@iph.ma.nsc.ru. Obut T. A.

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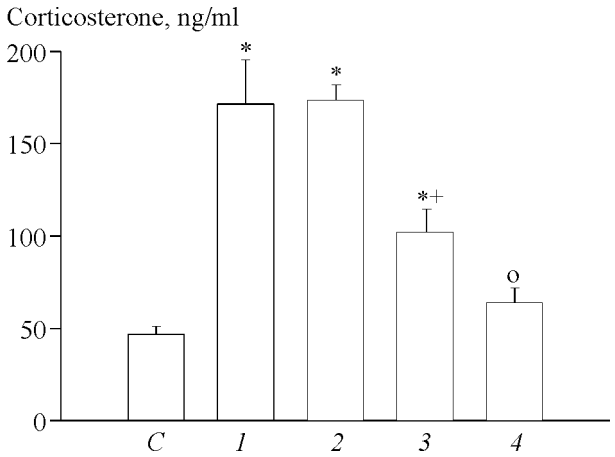

Fig. 1. Plasma concentration of corticosterone in male rats after single and repeated (19 days) stress exposure and administration of dehydroepiandrosterone sulfate (DHEAS): control (*C*), acute stress (*1*), acute stress and DHEAS (*2*), 19-day stress (*3*), 19-day stress and DHEAS (*4*). **p*<0.001 compared to the control; +*p*<0.01 compared to acute stress; °*p*<0.05 compared to 19-day stress.

DHEAS ($p>0.05$, Fig. 1). Our results indicate that DHEAS modulates stress reactivity and abolishes the stress-induced increase in corticosterone concentration. This effect of DHEAS was observed only after repeated stress exposure. This was probably related to activation of DHEA and DHEAS secretion in the zona reticulata of the adrenal glands [2,3].

An impressive body of evidence indicates that the opioid system is involved in stress reaction. However, there is no agreement regarding the role of this system during physiological and pathological stress and adaptation. Most authors believe that the opioid system suppresses the response of HPACS to stress and, therefore, abolishes stress-induced hyperactivity of its major components [1,9-13]. Published data show that opioid receptors are involved in these regulatory processes [1,6,8]. The role of individual opioid receptors in stress and adaptation remains unclear. Probably, μ- and δ-opioid receptors attenuate the response of HPACS to stress [1,9]. We found no published data on the effect of DHEAS on μ- and δ-opioid receptors. It was shown that DHEAS binds to σ-opioid receptors in the hippocampus [14]. Naltrexone in low doses (0.1-0.3 mg/kg) selectively blocks μ-opioid receptors, while in high doses (0.5-1.0 mg/kg) this agent blocks δ- and κ-opioid receptors [7].

In animals subjected to repeated stress and receiving 0.1 mg/kg naltrexone the concentration of corticosterone increased to a level observed in stressed animals not treated with DHEAS (Fig. 2). Corticosterone concentration in rats receiving naltrexone and DHEAS was much higher than animals injected with DHEAS alone ($p<0.05$). In rats subjected to acute stress administration of naltrexone in the same dose 20 min before treatment with DHEAS had no effect on corticosterone level (compared to other groups, Fig. 3).

Our results suggest that the effect of DHEAS on male rats after repeated stress exposure is realized via the opioid mechanism and involves μ-opioid receptors.

This mechanism mediates the inhibitory action of DHEAS on the stress-induced increase in corticosterone level. DHEAS has no effect on stress reactivity in rats after acute stress, when μ-opioid receptors are not involved in the regulation of stress reactions. Probably, the μ-opioid mechanism mediating the stress-limiting effect of DHEAS progressively develops during repeated treatment. This mechanism underlies the inhibition of hormonal catabolic reactions initiated by prolonged stress exposure.

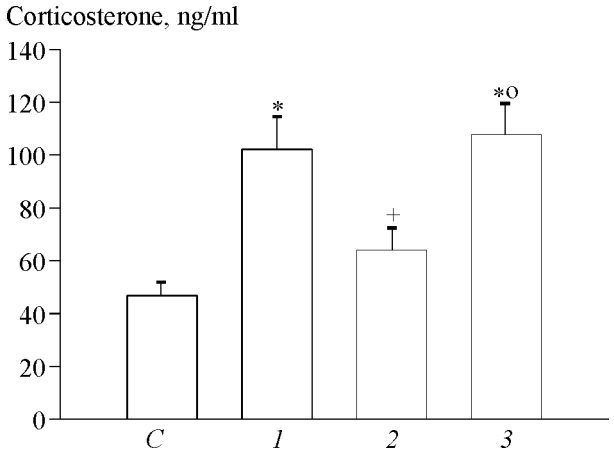

Fig. 2. Plasma concentration of corticosterone in male rats after 19-day stress and administration of DHEAS alone or in combination with naltrexone: control (*C*), 19-day stress (*1*), 19-day stress and DHEAS (*2*), 19-day stress+DHEAS+naltrexone (*3*). **p*<0.001 compared to the control; +*p*<0.05 compared to 19-day stress; °*p*<0.05 compared to 19-day stress and administration of DHEAS.

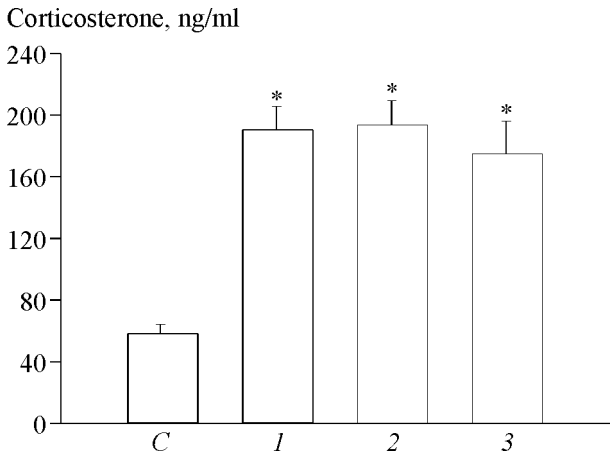

Fig. 3. Plasma concentration of corticosterone in male rats after acute stress and administration of DHEAS alone or in combination with naltrexone: control (*C*), acute stress (*1*), acute stress and DHEAS (*2*), acute stress+DHEAS+naltrexone (*3*). **p*<0.001 compared to the control.

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