Ratio between the Contents of 11-Dehydrocorticosterone and Corticosterone after Acute and Repeated Stress: Effect of Dehydroepiandrosterone Sulfate

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Acute stress was accompanied by reduction of 11-dehydrocorticosterone to corticosterone in male rats. The reverse reaction predominated during repeated stress and increased after administration of dehydroepiandrosterone sulfate. Treatment with μ-opioid receptor antagonist naltrexone in a dose of 0.1 mg/kg 20 min before administration of dehydroepiandrosterone sulfate abolished this effect.

Key Words: *11-dehydrocorticosterone; dehydroepiandrosterone sulfate; μ-opioid receptors; stress*

11-Dehydrocorticosterone (11-DCS) is a low-activity form of corticosterone. Transformation of corticosterone into 11-DCS is catalyzed by 11-β-hydroxysteroid dehydrogenase (11β-HSD). Changes in 11-DCS content during stress are poorly understood, because there were neither experimental objectives, nor methods for measureming 11-DCS content in small animals until recent time. Published data show that the adrenal hormone dehydroepiandrosterone sulfate (DHEAS) modulate 11β-HSD activity [6]. We found that DHEAS decreases stress reactivity in chronically stressed rats. The effect of DHEAS was estimated by changes in plasma corticosterone concentration and mediated by μ-opioid receptors [2].

Here we measured the ratio between the contents of 11-DCS and corticosterone during acute and repeated stress, studied the effect of DHEAS, and evaluated the role of opioid receptors in DHEAS-produced changes.

MATERIALS AND METHODS

Experiments were performed on male Wistar rats weighing 160-180 g. The rats were subjected to single or repeated 1-h shaking (once a day, 19 days) on an AVB-4p laboratory shaker at a frequency of 180 reciprocal motions per minute. Plasma corticosterone and 11-DCS were measured by high-performance liquid chromatography on a microcolumn. DHEAS was injected subcutaneously in a single dose of 30 mg/kg 2 days before decapitation. Selective μ-opioid receptor antagonist naltrexone was administered in a dose of 0.1 mg/kg 20 min before treatment with DHEAS [4]. The results were analyzed by Student's *t* test (Statistica software).

RESULTS

Acute stress was followed by a significant increase in plasma corticosterone level ($p<0.001$), but had no effect on 11-DCS concentration. The 11-DCS/corticosterone ratio significantly decreased ($p<0.05$, Fig. 1). Biosynthesis of these hormones during acute stress is directed towards the formation of corticosterone involved in the stress reaction.

Interconversion of corticosterone and 11-DCS is catalyzed by 2 isoforms of 11β-HSD: liver 11β-HSD I and kidney 11β-HSD II. These enzymes are present in various organs and tissues [10,13,14]. They catalyze both reduction and oxidation. 11β-HSD I catalyzes reduction of relatively inactive 11-DCS into cortico-

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sterone. 11β-HSD II converts active 11-hydroxycompounds into relatively inactive 11-ketosteroids (*i.e.*, corticosterone into 11-DCS) [10,12].

It can be hypothesized that acute stress is accompanied by activation of 11β-HSD I, which reduces relatively inactive 11β-DCS into active corticosterone. This hypothesis is confirmed by published data. In mice with genetic deficiency of 11β-HSD I acute restriction stress significantly increased the concentrations of both corticosterone and 11-DCS, whereas in normal mice the increase in corticosterone concentration was not accompanied by accumulation of 11-DCS [5]. These changes in the corticosterone/11-DCS ratio can result from not only activation of 11β-HSD I, but also the decrease in 11β-HSD II activity during acute stress [11].

Corticosterone level in rats exposed to repeated stress for 19 days significantly surpassed the control ($p<0.001$), but was much lower than in animals exposed to acute stress ($p<0.01$, Fig. 1). Thus, repeated stress stimulated transformation of corticosterone into 11-DCS. It was probably related to activation of 11β-HSD II, which converts corticosterone into 11-DCS and/or decreases activity of 11β-HSD I catalyzing the reverse reaction.

Changes in 11β-HSD activity during chronic stress are poorly studied. It was reported that chronic treatment decreased 11β-HSD I activity in the liver [7].

Our previous studies showed that 19-day shaking of male rats reduces stress reactivity [1]. Probably, transformation of corticosterone into low-activity 11-DCS contributes to adaptation to chronic stress and protects the organism from long-lasting effect of catabolically active glucocorticoids in high concentration. This assumption is confirmed by published data that 11β-HSD is colocalized with glucocorticoid and mineralocorticoid receptors in corticosterone target tissues and protects them from hormone excess [8,9,12].

In repeatedly stressed rats receiving DHEAS the level of corticosterone was much lower than in animals exposed to acute stress or 19-day treatment without administration of DHEAS. In these rats corticosterone concentration did not differ from normal (Fig. 1). DHEA decreases the degree of stress reactivity in repeatedly stressed animals, which is consistent with published data [2]. 11-DCS concentration did not dif-

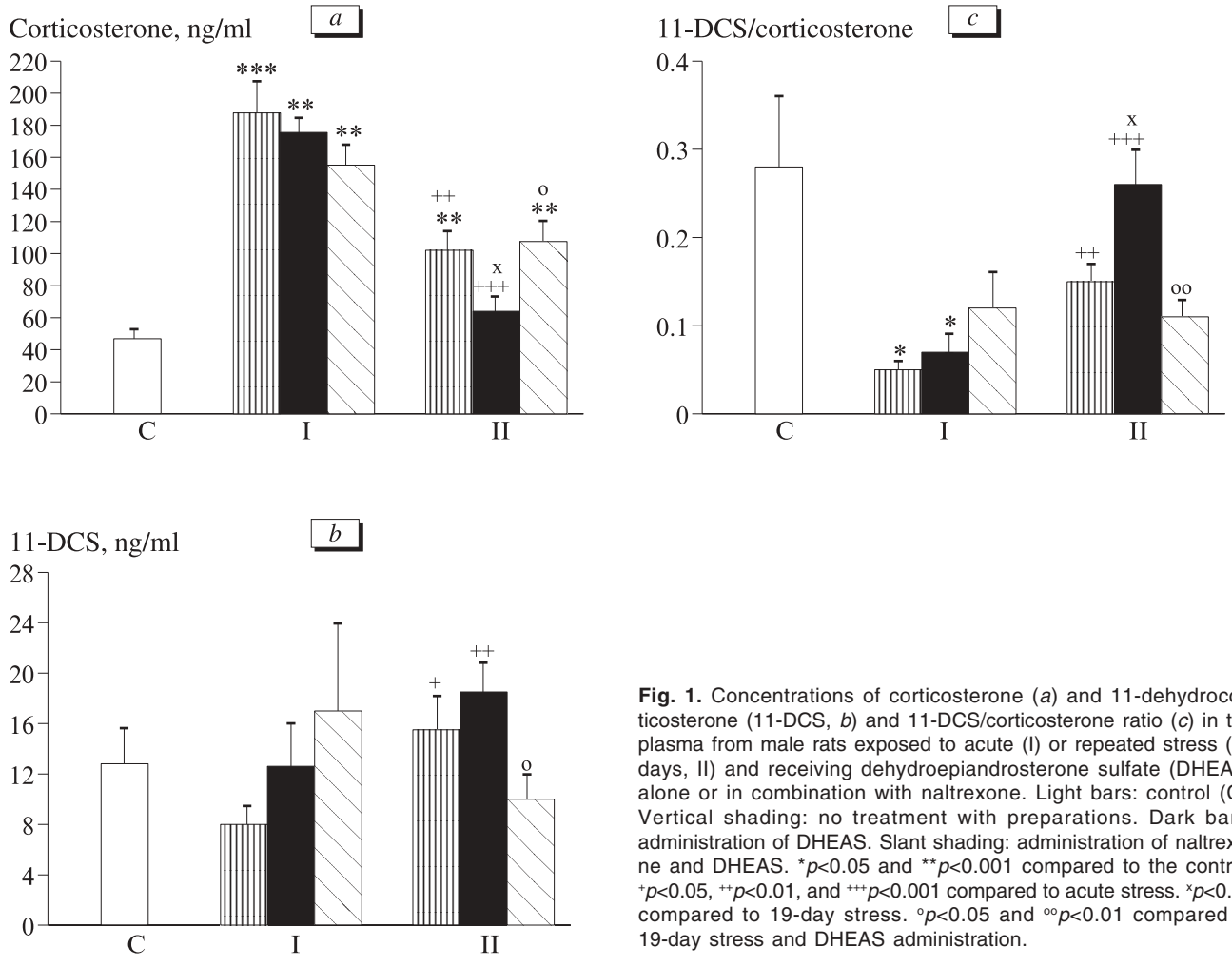

Fig. 1. Concentrations of corticosterone (*a*) and 11-dehydrocorticosterone (11-DCS, *b*) and 11-DCS/corticosterone ratio (*c*) in the plasma from male rats exposed to acute (I) or repeated stress (19 days, II) and receiving dehydroepiandrosterone sulfate (DHEAS) alone or in combination with naltrexone. Light bars: control (C). Vertical shading: no treatment with preparations. Dark bars: administration of DHEAS. Slant shading: administration of naltrexone and DHEAS. $^{*}p<0.05$ and $^{**}p<0.001$ compared to the control. $^{+}p<0.05$, $^{++}p<0.01$, and $^{+++}p<0.001$ compared to acute stress. $^{x}p<0.05$ compared to 19-day stress. $^{o}p<0.05$ and $^{oo}p<0.01$ compared to 19-day stress and DHEAS administration.

fer in repeatedly stressed rats receiving and not receiving DHEAS ($p>0.05$), but surpassed that in animals exposed to acute stress ($p<0.01$). The 11-DCS/corticosterone ratio in repeatedly stressed rats receiving DHEAS was much higher than in animals exposed to chronic ($p<0.05$) or acute stress without DHEAS treatment ($p<0.001$). These data show that DHEAS increased the intensity of corticosterone transformation into 11-DCS.

This effect of DHEAS is probably related to modulation of 11β-HSD activity. DHEAS increased kidney 11β-HSD II activity, but decreased liver 11β-HSD I activity in hypertensive SHR rats. These changes were accompanied by a decrease in the concentrations of corticosterone and 11-DCS and increase in the ratio between plasma levels of 11-DCS and corticosterone [6].

In our experiments administration of DHEAS to rats exposed to acute stress had no effect on the concentrations of corticosterone and 11-DCS and 11-DCS/corticosterone ratio (compared to animals not receiving DHEAS). DHEAS had no effect on transformation of corticosterone into 11-DCS and did not decrease stress reactivity during acute stress (as distinct from 19-day stress).

Blockade of μ-opioid receptors with naltrexone 20 min before administration of DHEAS abolished activation of corticosterone transformation into 11-DCS in repeatedly stressed rats, but had no effect in animals exposed to acute stress. It should be emphasized that DHEAS did not modulate stress reactivity in animals during acute stress. Therefore, DHEAS is involved in the regulation of corticosterone transformation into 11-DCS only under conditions of repeated stress. The effect of DHEAS is mediated by μ-opioid receptors. These data are consistent with the results of our previous experiment. We revealed that DHEAS protects the organism from adverse effects of chronic stress [2,3].

Our results show that acute stress is accompanied by reduction of relatively inactive 11-DCS into corticosterone. DHEAS had no effect on this reaction. The reverse reaction (transformation of corticosterone into 11-DCS) dominated during repeated stress and increased after administration of DHEAS. μ-Opioid receptor blockade with naltrexone abolished the activating effect of DHEAS on transformation of corticosterone into 11-DCS during repeated stress. These data indicate that the stimulating effect of DHEAS on transformation of corticosterone into 11-DCS is mediated by the μ-opioidergic regulatory mechanism.

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