Effect of Dehydroepiandrosterone Sulfate on Aldosterone Level during Stress Exposures: Role of μ-Opioid Receptors

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Dehydroepiandrosterone sulfate (DHEAS, 30 mg/kg) blocks stress-induced elevation of aldosterone concentration in rats subjected to repeated stress. Administration of DHEAS together with opioid receptor antagonist naltrexone in a dose of 0.1 mg/kg, *i.e.* the dose that selectively blocks μ-opioid receptors, abolished this blocking effect of DHEAS, which suggests that it is mediated by μ-opioid receptors. Under conditions of cold exposure, DHEAS exhibits the aldosterone-blocking effect even after single presentation of the stress factor. However, this effect is realized not via μ-opioid receptors, which attests to differences in the regulatory mechanisms depending on the nature of the external factor.

Key Words: *dehydroepiandrosterone sulfate; aldosterone; naltrexone; stress influences*

Stress influences induce an increase in blood aldosterone concentration [8] aimed at elevation of blood pressure and preparing the organism to aggression or run away. These processes are initiated by the stress-reaction and related changes in the regulatory and electrolyte balances in the body. We previously showed that dehydroepiandrosterone sulfate (DHEAS), an androgen produced by the adrenal glands, produces a stress-limiting effect realized via the central μ-opioid receptors (OR) [1,2]. The effects of DHEAS on aldosterone content, specifically under conditions of acute and chronic stress are little studied.

Here we studied the variations in aldosterone content and effect of DHEAS administration on this parameter during single and repeated stress exposures (SE) and evaluated possible role of μ-OR in the effects of DHEAS.

MATERIALS AND METHODS

Experiments were carried out on female Wistar rats weighing 160-240 g. Experimental groups consisted of 5-33 animals. The animals were kept under standard conditions in a vivarium of Institute of Physiology, Siberian Division of the Russian Academy of Medical Sciences with free access to food and water. Intact rats served as the control. Single (1 h) and repeated (for 19 days, 1 h per day) SE consisted of cold exposure (4°C) and shaking on an AVB-4p laboratory shaker (180 shakes per min). Plasma aldosterone content in systemic circulation was measured after SE by radioimmunoassay using standard kits. DHEAS (Sigma) was injected subcutaneously in a dose of 30 mg/kg 2 day before decapitation. Naltrexone (Sigma) was injected subcutaneously in a dose of 0.1 mg/kg 20 min before DHEAS.

The data were processed statistically using Student *t* test. The differences were significant at $p \leq 0.05$.

RESULTS

In control animals, administration of DHEAS and naltrexone did not significantly affect the plasma levels of aldosterone (Fig. 1).

Single cold SE significantly increased the level of aldosterone in comparison with the control ($p<0.001$). Administration of DHEAS reduced ($p<0.01$) the ele-

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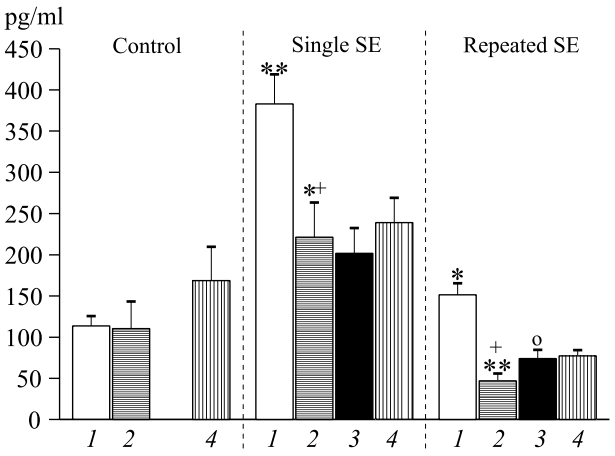

Fig. 1. Plasma aldosterone content in rats subjected to single or repeated cold SE. Here and in Fig. 2: 1) without drugs; 2) DHEAS; 3) naltrexone+DHEAS; 4) naltrexone. *$p \leq 0.05$, **$p < 0.001$ in comparison with controls receiving no preparations; $^{+}p < 0.01$ in comparison with rats of the same subgroup receiving no preparations; $^{o}p = 0.05$ in comparison with rats of the same subgroup receiving DHEAS.

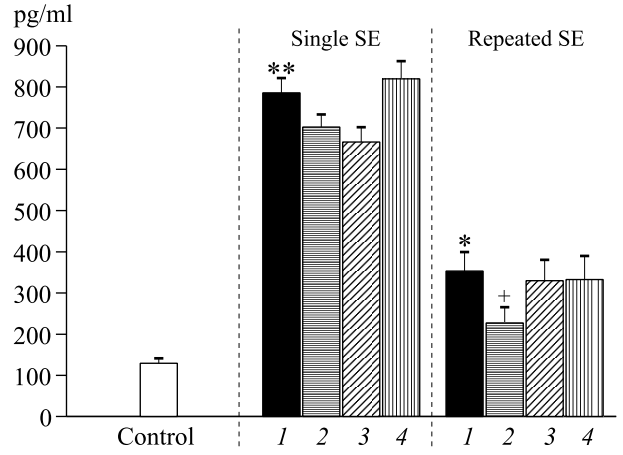

Fig. 2. Plasma aldosterone content in rats subjected to single or repeated shaking SE. *$p < 0.01$, **$p < 0.001$ in comparison with the control; $^{+}p = 0.05$ in comparison with rats of the same subgroup receiving no preparations.

vated concentration of aldosterone, but it still surpassed the control level ($p < 0.05$).

After repeated cold SE, blood aldosterone content also increased ($p = 0.05$), but significantly ($p < 0.001$) less markedly than after single cold SE (Fig. 1). This can be a result of habituation to stereotypically presented stress factor. Since aldosterone produces a hypertensive effect in the body [5,6], the less pronounced increase in aldosterone content during repeated cold SE can reflect an attenuation of the hypertensive effect of aldosterone. Administration of DHEAS to rats in this case, similarly to single cold SE, significantly ($p < 0.01$) reduced the cold-induced increase in aldosterone content to a level that was below the control ($p < 0.001$). It can be hypothesized that blood pressure also decreased against the background of DHEAS administration. It seems that the combination of repeated moderate cold SE and DHEAS administration can be used in clinical practice as a therapeutic measure for patients with hypertension of the aldosterone-renin-angiotensin genesis.

Administration of DHEAS with naltrexone in a dose of 0.1 mg/kg (selectively blocking μ-OR) abolished ($p = 0.05$) the DHEAS-induced decrease in aldosterone level in repeated, but not single cold SE. Hence this effect of DHEAS in case of repeated SE is realized via μ-OR. In single cold SE, the aldosterone-lowering effect of DHEAS is not mediated by μ-OR. Moreover, this reflects the peculiarities of the involvement of the opioid system into the regulatory process depending on the nature of external influence (acute or chronic).

We previously demonstrated the hypotensive effects of DHEAS [3] on hypertensive HSIAH rats. Here we can explain this hypotensive effect of DHEAS by its capacity to reduce the level of hypertensive hormone aldosterone, at least under conditions of cold SE, through μ-OR. It is noteworthy that the aldosterone-lowering effect of DHEAS under conditions of single cold SE was mot mediated by μ-OR.

Repeated shaking SE significantly increased plasma aldosterone concentration in rats ($p < 0.01$; Fig. 2). Administration of DHEAS significantly ($p = 0.05$) attenuated this SE-induced effect. Administration of naltrexon together with DHEAS restored the concentration of aldosterone to a level observed after shaking SE without drug administration. Hence, aldosterone abolished the aldosterone-lowering effect of DHEAS. Since naltrexone selectively blocks μ-OR [4], the observed abolition of the aldosterone-lowering effect of DHEAS is realized via μ-OR. Additional control with administration of naltrexone alone to animals exposed to repeated shaking SE had no appreciable effect.

Single shaking SE induced a sharp increase ($p < 0.001$) in aldosterone level, more pronounced ($p < 0.01$) than repeated SE. However, administration of DHEAS under these conditions, in contrast to single cold SE and repeated shaking SE, did not suppress the stress-induced increase in aldosterone level. Administration of naltrexone alone and in combination with DHEAS also was ineffective.

Thus, DHEAS produced a μ-OR-mediated blocking effect on stress-induced increase in aldosterone level in rats under conditions of repeated shaking SE. However, in single shaking SE (in contrast to single cold SE) DHEAS was ineffective. This suggests that the mechanisms of realization of physiological functions and involvement of the opioid system depend on the type and nature of SE.

It can be hypothesized that the observed blocking effect of DHEAS is mediated by a feedback mecha-

nism (suppression of steroid aldosterone by steroid DHEAS). In this case this negative relationship is realized via μ-OR. However, we found no published data confirming this possibility. Moreover, the results obtained by us in experiments with single shaking SE, where DHEAS was ineffective, contradict this assumption. In case this negative feedback does exist, it should manifest in both single and repeated SE. In controls, DHEAS also did not decrease aldosterone content. It can be hypothesized that this effect of DHEAS cannot be explained by the negative feedback, but is determined by *de novo* formation of a certain regulatory μ-opioid mechanism precisely in repeated SE that is characterized by and requires gradual induction [4,7].

The stress-induced increase in blood level of aldosterone that produces a hypertensive effect in the body [5,6] and elevates BP preparing the organism to either fighting, or runaway is a phylogenetically developed adaptive mechanism. However, long-term maintenance of elevated BP in case of long-term SE can be dangerous. That is why the μ-opioid mechanism blocking the stress-induced increase in aldosterone level and the corresponding BP elevation with participation of DHEAS should be regarded as an adaptive mechanism. This phenomenon can be used in clinical practice.

Our findings suggest that DHEAS blocks the stress-induced increase in aldosterone level in rats under conditions of repeated SE provoked by cold or shaking and that this effect is realized via μ-OR. Under conditions of cold exposure, DEAS exhibits an aldosterone-blocking effect even after single presentation of the stress factor. However, this effect is realized not via μ-OR, which attests to differences in the involved regulatory mechanisms depending on the nature of the external factor.

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