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DHEA administration modulates stress-induced analgesia in rats

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HIGHLIGHTS

- We evaluated the effect of DHEA on stress-induced analgesia in rats.
- Acute treatment with DHEA had the same effect as the exposure to acute stress.
- The treatment with DHEA prolongs acute stress-induced analgesia.

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ABSTRACT

An important aspect of adaptive stress response is the pain response suppression that occurs during or following stress exposure, which is often referred to as acute stress-induced analgesia. Dehydroepiandrosterone (DHEA) participates in the modulation of adaptive stress response, changing the HPA axis activity. The effect of DHEA on the HPA axis activity is dependent on the state and uses the same systems that participate in the regulation of acute stress-induced analgesia. The impact of DHEA on nociception has been studied; however, the effect of DHEA on stress-induced analgesia is not known. Thus, the aim of the present study was to evaluate the effect of DHEA on stress-induced analgesia and determine the best time for hormone administration in relation to exposure to stressor stimulus. The animals were stressed by restraint for 1 h in a single exposure and received treatment with DHEA by a single injection before the stress or a single injection after the stress. Nociception was assessed with a tail-flick apparatus. Serum corticosterone levels were measured. DHEA administered before exposure to stress prolonged the acute stress-induced analgesia. This effect was not observed when the DHEA was administered after the stress. DHEA treatment in non-stressed rats did not alter the nociceptive threshold, suggesting that the DHEA effect on nociception is state-dependent. The injection of DHEA had the same effect as exposure to acute stress, with both increasing the levels of corticosterone. In conclusion, acute treatment with DHEA mimics the response to acute stress indexed by an increase in activity of the HPA axis. The treatment with DHEA before stress exposure may facilitate adaptive stress response, prolonging acute stress-induced analgesia, which may be a therapeutic strategy of interest to clinics.

1. Introduction

Individuals exposed to threatening situations (stressor) present physical and behavioral changes (stress response) with the objective of maintaining homeostasis [1, 2, 3]. Stress responses mainly include activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, and induction of the corticotropin-releasing hormone (CRH) and vasopressin (VP) by parvocellular neurons of the paraventricular nucleus of the hypothalamus (PVN) [2]. CRH acts on the anterior pituitary gland, releasing adrenocorticotrophic hormone (ACTH), which in turn stimulates the release of glucocorticoids by the adrenal cortex. During the stress response, the PVN receives information from brainstem afferents, among them the locus coeruleus, an ascending noradrenergic pathway with an important role in HPA activation [4], inducing an increase in the synthesis of CRH and VP [5, 6]. The PVN is a central integrator of endocrine, vegetative and behavioral responses [2].

An important aspect of the adaptive stress response is the pain response suppression that occurs during or following stress exposure. It contributes to the expression of appropriate behaviors to face stressors,

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facilitating the responses of fight or flight [7, 8]. This phenomenon is often referred to as stress-induced analgesia (SIA), and occurs in both laboratory animals and humans [7, 8]. SIA involves activation of the descending inhibitory pain pathway, originating in the neurons of the cortex, hypothalamus and amygdala, and project into the periaqueductal gray and rostroventral medulla and finally to the dorsal horn of the spinal cord. Activation of this pathway results in an inhibitory effect at the level of the dorsal horn by inhibiting the ascending transmission of nociceptive information [7]. It is known that acute stress-induced analgesia involves the modulation of opioid receptors [9] and nonopioid receptors (e.g. NMDA and GABA receptors) [10]. In addition, corticosterone can facilitate analgesia induced by stress, since this phenomenon may be blocked by adrenalectomy and reestablished by treatment with the administration of corticosterone [7].

Another hormone that participates in the modulation of adaptive stress response is the adrenal hormone dehydroepiandrosterone (DHEA). DHEA is considered a neuroactive steroid, and a crucial endogenous modulator of numerous physiological functions [11, 12]. The main biological functions of DHEA on the nervous system are neuroprotection, catecholamine synthesis and secretion, as well as antioxidant and anti-inflammatory activities [12]. DHEA has been shown to modulate various receptors, such as GABA(A), N-methyl-D-aspartate (NMDA), kainate, ionotropic glutamate, nicotinic acetylcholine, muscarinic, glycine, σ1 and neurotrophin receptors and ionic channels such as calcium, sodium and potassium channels [13, 14]. In humans, elevated levels of DHEA have been observed in response to stress exposure [13]. DHEA may be secreted in response to ACTH in humans at least [15], and it modulates HPA axis activity [16, 17]. In an in vitro study, ACTH-induced corticosterone release by rat adrenal zona fasciculate-reticularis cells was attenuated by DHEA [18]. During repeated stress exposure, a single injection of DHEA can reduce the serum corticosterone levels [17]. On the other hand, it was observed that a single injection of DHEA stimulates the secretion of hypothalamic CRH, ACTH by the pituitary and corticosterone by the adrenal cortex in nonstressed rats [16]. In addition, chronic DHEA treatment increases CRH mRNA levels in hypothalamic PVN independent of age and sex in nonstressed rats [19], suggesting that the effect of DHEA on the HPA axis activity is dependent on state.

The impact of DHEA on nociception has been studied [20, 21], although it is still not well understood. DHEA effects on nociceptive mechanisms are complex. Acute DHEA treatment exerts a biphasic effect on nociception (a rapid pro-nociceptive action and a delayed anti-nociceptive effect). On the other hand, chronic treatment with DHEA elevates the nociceptive threshold [21, 22]. However, the effect of DHEA on stress-induced analgesia is not known.

SIA may be thought of as an important component of the fight or flight response [7]. The understanding of the fundamental mechanism of pain suppression that occurs during or following exposure to stress and how this effect can be modulated becomes a potential new therapeutic target for pain and stress-related disorders. Thus, the aim of the present study was to evaluate the effect of DHEA on stress-induced analgesia and determine the best time for hormone administration in relation to exposure to stressor stimulus.

2. Material and methods

2.1. Animals

Male adult Wistar rats (60–70 days, mean weight 300 g) were obtained from the Center for Laboratory Animal Reproduction and Research (CREAL) at the Universidade Federal do Rio Grande do Sul (UFRGS). The number of animals was four rats per cage with food and water available ad libitum and they were maintained in a 12 h light/dark cycle (lights on at 7:00 a.m. and lights off at 7.00 p.m.) in a humidity- and temperature-controlled environment (22 ± 2 °C). Initially, the rats were divided into four animals per cage and acclimated to the vivarium for one week before beginning treatment. After the acclimation period, the animals were randomly selected by weight and subsequently divided into a control group (rats were housed only with other control rats) and stress group (rats that underwent restraint stress were housed only with other rats that underwent restraint stress). They were handled for 14 days prior to the experiments. All experiments and procedures were approved by the Institutional Animal Care and Use Committee (CEUA-UFRGS protocol No. 19788) and were compliant with Brazilian guidelines involving the use of animals in research (Law No. 11.794). Additionally, all efforts were made to minimize the suffering, pain and discomfort of the animals, as well as to reduce the number of animals. The animals were euthanized 15 min after the last measure of TFL and the trunk blood collected. Death by decapitation was carried out by a trained professional and in a separate room to where they were experiencing stress and treatment.

2.2. Stress procedures

The animals were stressed by restraint for 1 h in a single exposure [23]. Restraint stress was carried out by placing each animal in a 25 × 7 cm plastic tube, and adjusting it with plaster tape on the outside so that the animal was unable to move. There was a 1 cm hole in the far end for breathing. Control animals were manipulated, but not submitted to restraint. Stressed animals were submitted to a single exposure to the restraint. The immobilization procedure was carried out between 1000 and 1200 h a.m.

2.3. Treatment

Each group (stressed and control) was subdivided into three treatment groups (n = 7–8 per group): 1) injection of DHEA 30 min before the stress and injection of vehicle 30 min after the stress; 2) injection of vehicle 30 min before the stress and injection of DHEA 30 min after the stress; and 3) injection of vehicle 30 min before the stress and injection of vehicle 30 min after the stress (Fig. 1). Animals received DHEA (Calbiochem) as a single i.p. dose of 25 mg/kg diluted in 20% cyclodextrin.

2.4. Tail-flick measures

Nociception was assessed with a tail-flick apparatus. Rats were wrapped in a towel and placed on the apparatus. A photo beam with adjustable sensitivity detects the tail flick and the latency is automatically presented on a digital display on the control unit. The light source positioned below the tail was focused on a point 2.3 cm rostral to the tip of the tail. Deflection of the tail activated a photocell and automatically terminated the trial. Light intensity was adjusted to obtain the baseline tail-flick latency (TFL) of 4–6 s as described in the manufacturer's protocol (LE7106 Tail-flick Meter/Harvard Apparatus). Measurements of reaction time are given with a 0.1 second precision. Once this intensity had been established, rats with baseline latency >7 s and <3 s were excluded from the experiment. A cutoff time of 10 s was used to avoid tissue damage. The groove system for the tail and the adjustment of response sensitivity ensure optimum repeatability and reliability of results. The general procedure was as follows [23, 24]: Day 1, the animals were familiarized with the apparatus; day 2, the baseline TFL value was obtained; day 3, animals were subjected to three TFL measurements for the analgesia test. The first TFL measurement was taken 15 min after the first injection, the second immediately after stress and the third 15 min after the second injection (Fig. 1).

2.5. Corticosterone serum concentration

The rats were killed and trunk blood samples were collected in tubes containing clot activator gel (BD, Vacutainer®). After centrifugation at