Analgesic Effect of Corticotropin-Releasing Hormone: Involvement of the Hypothalamic-Pituitary-Adrenocortical Axis into Its Realization

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Involvement of hypothalamic-pituitary-adrenocortical axis into the analgesic effect of corticotropin-releasing hormone after its systemic administration was studied in experiments on rats. Pharmacological blockade of the hypothalamic-pituitary-adrenocortical axis decreased the duration and degree of the analgesic effect of corticotropin-releasing hormone. This analgesic effect can be mediated via two pathways: related to hormones of the hypothalamic-pituitary-adrenocortical axis and independent of these hormones.

Key Words: *corticotropin-releasing hormone; nociception; corticosterone; opioid receptor; rat*

Analgesia is a manifestation of organism's reaction to stress. Activation of the hypothalamic-pituitary-adrenocortical axis (HPACA) is a necessary condition for the development of nonopioid analgesia during stress [5]. The involvement of ACTH and glucocorticoids into nociception was previously demonstrated [1,2,4,13-15]. Corticotropin-releasing hormone (CRH) exerts an analgesic effect via stimulation of ACTH synthesis [10,11]. However, the mechanism of the analgesic action of CRH remains unclear. The role of HPACA and opioid system in CRH-induced analgesia was not examined. Systemic administration of CRH can produce the analgesic effect via opioid receptors [7] and via mechanisms not related to the opioid system [6].

Our aim was to study the involvement of HPACA and opioid system into the analgesic effect of systemically administered CRH.

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MATERIALS AND METHODS

Experiments were carried out on male Sprague--Dawley rats weighing 200-300 g. CRH (Serva) was injected intraperitoneally in a dose of 40 mg/kg. Elevation of plasma glucocorticoids was comparable to that produced by stress. Controls were injected intraperitoneally with physiological saline. The effect of CRH on nociception was examined in rats with intact and inhibited HPACA. Blockade of HPACA was produced by intraperitoneal injection of hydrocortisone (Richter, 300 mg/kg) 1 week before testing the nociceptive function; 1 week after injection hydrocortisone was absent in the blood. For evaluation of the role of the opioid system in the analgesic effect of CRH, this enzyme was injected to rats after blockade of opioid receptors with naltrexone (1 mg/kg intraperitoneally) 15 min before recording of the initial nociceptive threshold.

The state of HPACA and pain sensitivity were examined simultaneously. To avoid uncontrolled stressor stimuli, nociceptive function was tested on slightly anesthetized animals [1-3,5,8,9]. The experiments were made under nembutal narcosis (40 mg/kg intraperitoneally), which was administered

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20 min before recording of the nociceptive threshold. Pain sensitivity was assessed by the threshold of tail-flick response caused by electric stimulation of the tail performed before injection of CRH and on minutes 3, 8, 15, 20, and 30 postinjection. The nociceptive threshold was measured by the minimum amplitude of the current inducing the tail-flick response. To this end, the sinusoidal current was applied at 500 Hz, the amplitude was changed from 0.07 to 2 mA with 70 μA steps. Then the rats were decapitated, and plasma corticosterone was measured by spectrofluorometry.

The data were processed statistically using Student's *t* test or its modifications for discriminate dispersions. The nociceptive thresholds were analyzed using Mann—Whitney *U* test.

RESULTS

Systemic injection of CRH to rats with intact HPACA rapidly elevated the nociceptive threshold. This elevation began on postinjection minute 3 and lasted for more than 30 min (Fig. 1). On minute 30 postinjection, plasma corticosterone was 25.5± 2.3 μg/dl (n=19) compared to 4.9±0.7 μg/dl (n=19) in control rats injected with physiological saline.

Preliminary injection of hydrocortisone inhibited HPACA. In these rats, plasma level of corticosterone was 4.4±0.3 μg/dl (n=16) or 4.7±0.3 μg/dl (n=15) on minute 30 after injection of CRH or physiological saline, respectively. Inhibition of HPACA decreased the duration of CRH-induced analgesic effect (it was observed only from minute 8 to minute 15 postinjection); the effect was also less pronounced: the nociceptive thresholds were significantly lower in rats with inhibited HPACA than in rats with intact HPACA (Fig. 2).

Injection of opioid antagonist produced no significant changes in the analgesic effect of CRH (Fig. 3). In rats treated with naltrexone, a significant elevation of the nociceptive threshold was observed starting from minute 3, but the nociceptive threshold measured on minute 3 was lower than on minute 8 (next measurement). This peculiarity indicates relative decrease of the first (rapid) phase of CRH-induced response in rats with blocked opioid receptors. The opioid antagonist produced no effect on the plasma level of corticosteroids. In naltrexone-treated rats, elevation of plasma corticosterone on minute 30 after injection of CRH or solvent was 22.1±2.5 μg/dl (n=9) and 3.7±0.5 μg/dl (n=8), respectively.

Thus, systemic injection of CRH inhibited the nociceptive response triggered by electric stimulation of rat tail.

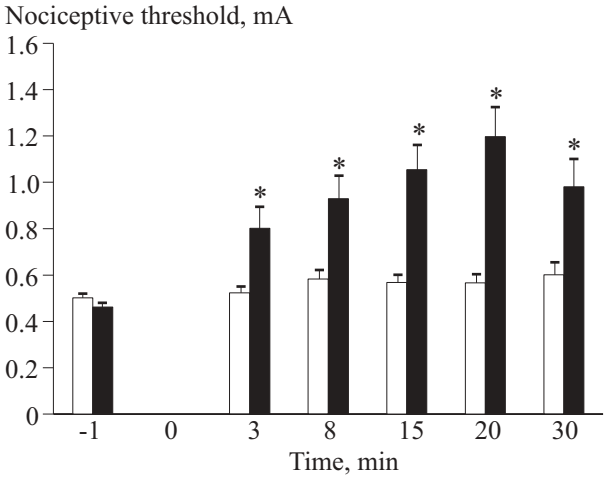

Fig. 1. Effect of corticotropin-releasing hormone (CRH) on nociception in rats with normal production of hormones by the hypothalamic-pituitary-adrenocortical axis (HPACA). Open and solid bars show nociceptive threshold after injection of physiological saline (n=18-19) and CRH (n=18-19), respectively. Here and in Figs. 2, 3: zero time corresponds to the moment of injection. *p<0.05 compared to the tests with physiological saline.

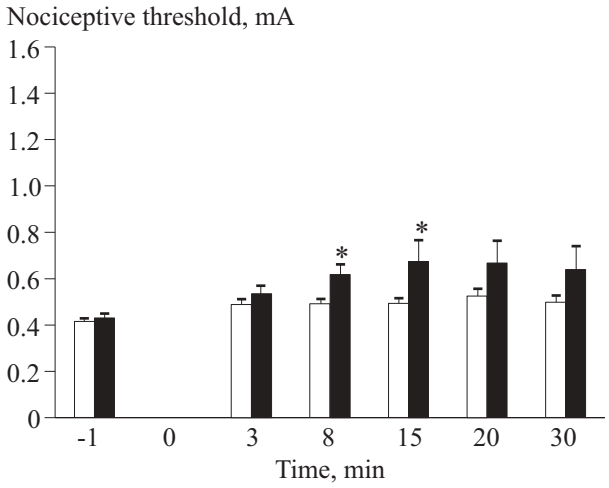

Fig. 2. Effect of CRH on nociception in rats with inhibited production of hormones by HPACA. The open and solid bars show the nociceptive threshold after injection of physiological saline (n=13-15) and CRH (n=15-16), respectively.

The mechanism of CRH analgesia mediated via HPACA hormones was demonstrated during the entire observation period (from minute 3 to minute 30), which is attested by a decrease of the strength and duration of this analgesia in rats with inhibited HPACA. These data agree with previous conclusions on the involvement of glucocorticoids in the development of non-opioid forms of analgesia [3,4]. During the first minutes after injection, the action of CRH can be mediated not only by HPACA hormones, but also (to some extent) by opioids — probably, due to the release of ACTH, whose effect

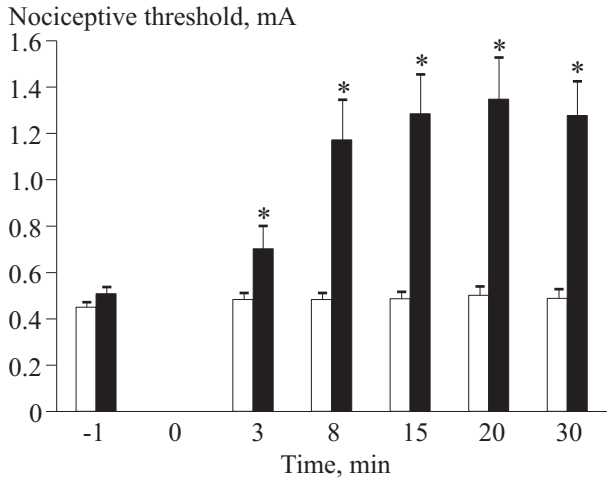

Fig. 3. Effect of naltrexone on CRH analgesia in rats with normal production of hormones by HPACA. Open and solid bars show nociceptive threshold after injection of physiological saline (*n*=8) and CRH (*n*=9-10), respectively.

on nociception during the first minutes postinjection is mediated via opioid receptors [3].

The mechanism of CRH analgesia, which is not related to ACTH and glucocorticoids, was observed from minute 8 to minute 15. Hypothetically, the analgesic effect of CRH observed in rats with inhibited HPACA resulted from its peripheral paracrine activity [12].

Therefore, CRH analgesia can be mediated by at least two mechanisms. One of them is related to glucocorticoids and ACTH, while the second mechanism does not depend on HPACA hormones.

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