Effect of ACTH on Pain Sensitivity in Rats

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Systemic administration of ACTH to rats with normal hormone production induced a rapid (started 3 min postinjection) and long-term (persisted 30 min) elevation of pain threshold. Complete inhibition of glucocorticoid production shortened the duration of ACTH-induced analgesia to 15 min. The biphasic effect of ACTH on pain sensitivity is probably mediated by short-term glucocorticoid-independent and long-term glucocorticoid-dependent mechanisms.

Key Words: *ACTH; pain sensitivity; hypothalamic-pituitary-adrenocortical system; corticosterone; rats*

The decrease in pain sensitivity is a typical nonspecific adaptive response to adverse environmental factors. The mechanisms underlying these changes involve hormones of the hypothalamic-pituitary-adrenocortical system (HPACS), a principal adaptation system in the body. The contribution of each element of HPACS into the regulation of pain sensitivity can be evaluated. Our previous studies showed that glucocorticoids produced by the adrenal cortex are involved in the development of stress-induced nonopioid analgesia [2]. The role of pituitary hormone ACTH in modulation of pain threshold remains unclear. Here we studied the role of the pituitary component of HPACS in the regulation of pain sensitivity.

MATERIALS AND METHODS

Experiments were performed on male Sprague—Dawley rats weighing 220-300 g. The animals were anesthetized with nembutal (4 mg/100 g body weight, intraperitoneally) 20 min before measurements of the initial pain threshold. Pain sensitivity was estimated by nociceptive reaction threshold before and 30 min after ACTH administration. Current strength (500 Hz sinusoidal current) inducing tail flick reaction was taken as the pain threshold. Current strength increased from 0.07 to 2 mA with a 70-μA intervals. To evaluated the role of the pituitary component of HPACS, ACTH was injected to rats with normal production of HPACS hormones and rats with partial or complete blockade of HPACS. Blockade of HPACS abolished the rise of blood glucocorticoid content in response to exogenous ACTH. Glucocorticoid deficiency was modeled by intraperitoneal injection of hydrocortisone in pharmacological doses (15 and 30 mg/100 g, Richter) 1 week before measurements of nociceptive reactions. ACTH (Serva) was injected intraperitoneally in a dose of 0.5 U/kg. This dose caused the rise of plasma glucocorticoid content similar to that observed under stress conditions. Control animals received physiological saline. The rats were decapitated, and plasma corticosterone content was measured spectrofluorometrically (micromethod). The results were analyzed by Student's *t* test or its modification (for different variances). Differences between pain thresholds were analyzed by Mann—Whitney test.

RESULTS

Systemic administration of ACTH to rats with normal hormone production induced a rapid (3 min postinjection) and long-term (30 min) increase in pain threshold (Fig. 1, *a*). This reaction was associated with ACTH-induced stimulation of glucocorticoid secretion, which increases pain threshold. Thirty minutes postinjection plasma corticosterone content in ACTH-treated (n=19)

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rats increased to 16.49±2.36 μg/100 ml *vs.* 3.08±0.59 μg/100 ml in the control (n=16). In animals with partial blockade of HPACS (n=21), plasma corticosterone content 30 min after ACTH injection was 7.47±1.16 μg/100 ml, *i.e.* 2-fold lower than in ACTH-treated rats with normal hormone production, but significantly differed from the control (3.15±0.71 μg/100 ml, n=19). Partial blockade of HPACS did not change the effect of ACTH on pain sensitivity: pain threshold in ACTH-treated animals did not differ from that in rats with intact HPACS (Fig. 1, *b*). Therefore, the 2-fold suppression of the ACTH-induced increase in plasma corticosterone content in rats with partial blockade of HPACS was not accompanied by changes in pain threshold. Thirty minutes after ACTH administration plasma corticosterone content in rats with complete blockade of HPACS (n=9) was 2.95±0.43 μg/100 ml, which did not significantly differ from the control (2.59±0.46 μg/100 ml, n=9). In rats with complete blockade of HPACS, ACTH-induced changes in pain threshold qualitatively differed from those in animals with intact or partially blocked HPACS (Fig. 1, *c*). Pain threshold increased 3 min after ACTH administration, markedly decreased 15 min postinjection (slightly but significantly surpassed the control) and returned to normal after 30 min. Thus, HPACS does not respond to ACTH by changes in glucocorticoid content, which shortens the duration of hormone-produced effects.

These data suggest that glucocorticoids are involved in ACTH-dependent modulation of pain sensitivity, which is consistent with published data on the role of these hormones in analgesic effects of stress during nonopioid analgesia and the dose-dependent relationship between blood glucocorticoid content and pain threshold. Experiments with partial blockade of HPACS demonstrated the mechanisms underlying effects of these hormones. Nociceptive reactions are realized if glucocorticoid content 2-fold surpasses the con-

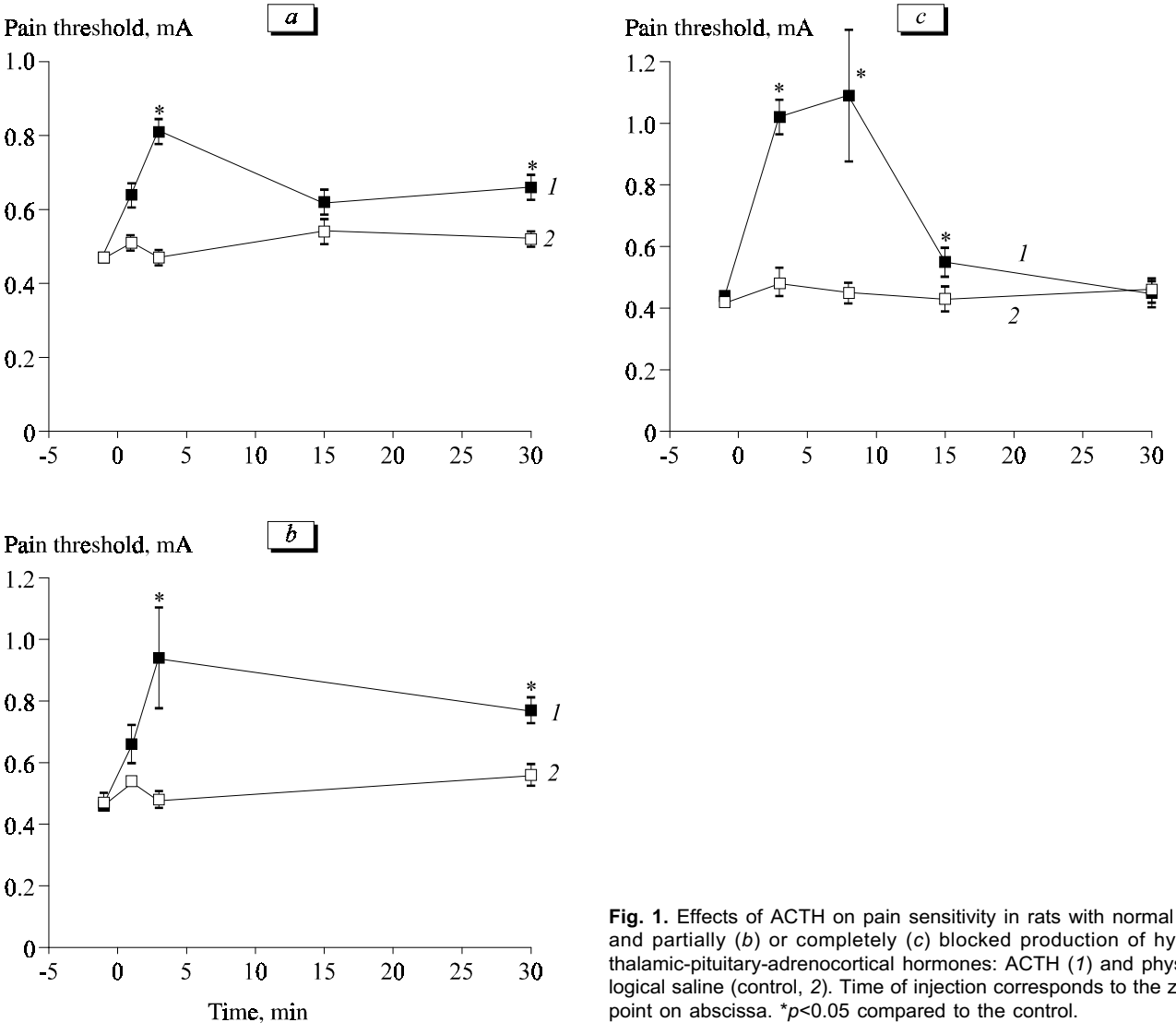

Fig. 1. Effects of ACTH on pain sensitivity in rats with normal (*a*) and partially (*b*) or completely (*c*) blocked production of hypothalamic-pituitary-adrenocortical hormones: ACTH (*1*) and physiological saline (control, *2*). Time of injection corresponds to the zero point on abscissa. *p<0.05 compared to the control.

trol level. This relationship between the pain threshold and glucocorticoid content is observed under stress conditions. Administration of ACTH to animals with complete blockade of HPACS inhibited the final stage of changes in pain sensitivity (30 min). These findings indicated that the initial stage of ACTH-induced changes in pain sensitivity (15 min) is not mediated by glucocorticoids (*i.e.*, ACTH directly affects pain sensitivity).

Published data show that systemic administration of ACTH causes hypoalgesia in rats [7]. In our experiments, pain threshold increased 30 min after intraperitoneal administration of 20 U/kg ACTH. The question arises: whether or not this effect of ACTH is mediated by glucocorticoids? ACTH-induced hypoalgesia was found in clinical observations [6]. However, there are data that ACTH has no effect on pain sensitivity. Systemic administration of ACTH in a daily dose of 20 μg to rats for 10 days did not modulate pain sensitivity [5]. Moreover, many authors reported a hyperalgesic effect of ACTH [8,9]. It was shown that hypophysectomy potentiates the analgesic effect [4], *i.e.*, the absence of ACTH enhances analgesia. These facts indirectly indicate that ACTH increases pain sensitivity. Experiments on mice showed that ACTH produces various effects (from hyper- to hypoalgesia) depending on its dose [3]. Thus, published data do not show the role of ACTH in the regulation of pain sensitivity.

Our findings indicate that ACTH produces an analgesic effect. This effect is biphasic and is probably mediated via short-term glucocorticoid-independent and long-term glucocorticoid-dependent mechanisms.

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