

LETTER TO THE EDITOR

FAILURE OF HYDROCORTISONE AND 2% SALINE TREATMENT TO ABOLISH MORPHINE AND STRESS-INDUCED ANALGESIA IN RATS

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It has been demonstrated that analgesia induced by physiological stress (1, 6) and electro-acupuncture (8) may be mediated through an endogenous opioid mechanism. It is also known that acute stressful stimuli cause a concomitant release of  $\beta$ -endorphin and adrenocorticotropin (ACTH) from the pituitary gland (4). Both these are peptides derived from a common precursor molecule (7) and the release of  $\beta$ -endorphin is also considered to be regulated by the same feedback system which is concerned with ACTH release (9). With these reports in view we have examined the effect of repeated injections of hydrocortisone (a treatment which inhibits ACTH-release) and of 2% saline-treatment, reported to deplete pituitary  $\beta$ -endorphin by 50% (3) on morphine - and heat stress-induced analgesia in rats. It was hoped that the study would indicate the relevance of endogenous opioid release in stress-induced analgesia.

Albino rats of either sex (150-200 g) maintained on free access to food and water were used. The room temperature was  $22 \pm 2^\circ\text{C}$  throughout the study.

Analgesic response (pain threshold to radiant heat) was measured in groups of rats using an analgesiometer; each group had a minimum of 5 rats. Baseline latencies to tail-flick withdrawal from the radiant heat source were established. A minimum of 5 trials were recorded for each animal at 2 min intervals before subjecting the animals to stress- or morphine-treatment. Animals were tested for analgesia immediately after stress (exposure to heat in a 'stress box' maintained at  $40 \pm 2^\circ\text{C}$  for 1 hr). After morphine-treatment (5 mg/kg, ip) analgesic responses were recorded at 30 min since preliminary experiments showed that maximal analgesic effect was seen at this time. 2% saline treatment consisted of administration 2% (w/v) NaCl solution in place of drinking water for 72 hr prior to subjecting them to either heat-stress or morphine-treatment. Hydrocortisone treatment consisted of administration of the drug (100 mg/kg/day, sc) for 5 days; the animals were used 1 hr after the last dose for administration of either heat stress or morphine-treatment. Statistical analysis was done using student's *t* test.

Acute heat stress for 1 hr or administration of morphine significantly increased pain threshold (Fig. 1). Treatment of animals with 2% saline or with hydrocortisone did not have any effect on the basal reaction time and this treatment also failed to modify morphine-induced analgesia. Similarly, 2% saline treatment failed to abolish stress-induced analgesia. However, hydrocortisone treatment partially but significantly abolished heat stress-induced analgesia in rats ( $P < 0.05$ ).

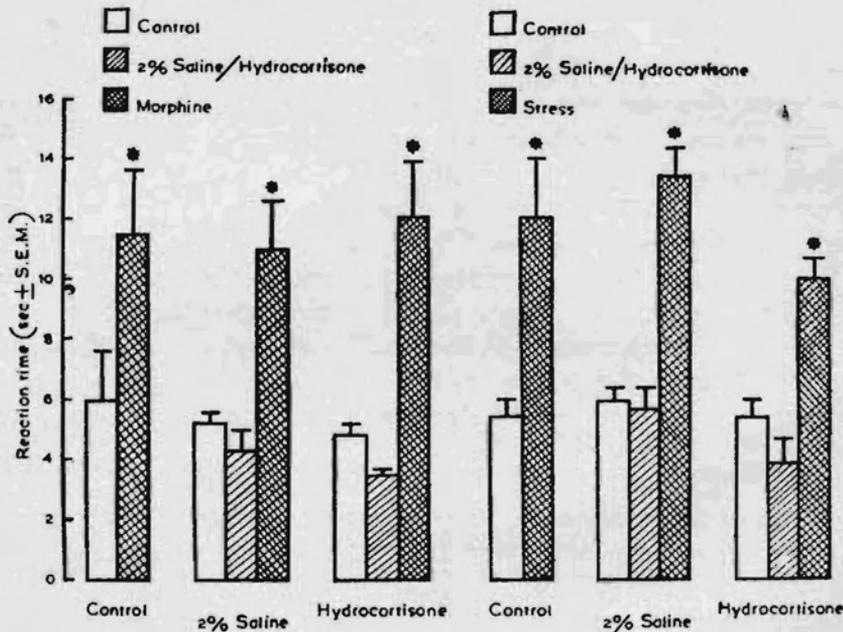


Fig. 1 : Analgesia induced by morphine (5 mg/kg, given ip 30 min before) and by heat-stress (exposure to heat,  $40 \pm 2^\circ\text{C}$  for 1 hr) in control rats and in rats chronically treated with hydrocortisone (100 mg/kg, sc, daily for 5 days) or 2% saline (substitution of drinking water by saline for 72 hr.). Each block shows mean reaction time (heat analgesiometry) with S.E.M. (vertical lines) obtained from 5 animals. \* Value significantly differs from control ( $P < 0.001$ ).

We have earlier reported that naloxone reverses heat stress-induced analgesia (5) indicating the role of endogenous opioids in stress-analgesia. The finding that heat stress-analgesia (but not morphine-analgesia) was partially ( $P < 0.05$ ) antagonised by hydro-cortisone treatment suggests that stress-analgesia is a complex reaction of the organism to stressful situation involving both pituitary and brain  $\beta$ -endorphin and that the treatment does not alter sensitivity of opioid receptors. The observations of Cheng *et al.* (3) and that of Bodnar *et al.* (2) regarding the ineffectiveness of feed back inhibition

of ACTH release or partial depletion of  $\beta$ -endorphin in altering electroacupuncture- and swim-induced analgesia supported the present observations. However, heat stress-induced analgesia appears to differ from electroacupuncture analgesia in that the partial depletion of pituitary  $\beta$ -endorphin caused by 2% NaCl treatment failed to effect stress analgesia. Possibly, the two types of stress-stimuli may have a different effect in these partially depleted animals as regards to the induction of analgesia. Despite the correlation between central opioid levels and pain responsiveness, opiate and stress analgesia remained unaffected in rats partially depleted of their pituitary  $\beta$ -endorphin. This suggests that the depletion also does not alter sensitivity of opioid receptor and that the pituitary opioid is not solely responsible for the full expression of stress analgesia (2).

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