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BRIEF COMMUNICATION

Beta-Endorphin is Behaviorally Active in Rats After Chronic Intravenous Administration

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GORELICK, D. A., D. H. CATLIN, R. GEORGE AND C. H. LI. *Beta-endorphin is behaviorally active in rats after chronic intravenous administration.* PHARMAC. BIOCHEM. BEHAV. 9(3) 385–386, 1978.—Male Sprague-Dawley rats received 14 daily intravenous injections of saline or human beta-endorphin (2.5 mg/kg). Animals were given one-way active avoidance training on the eleventh day, and analgesia testing on the twelfth (tail-flick) and thirteenth (hot-plate) days. Beta-endorphin had no effect on the number of trials needed to reach the avoidance criterion, but significantly lengthened response latencies. Beta-endorphin had no analgesic effect in either test procedure.

Endorphin Behavior Intravenous activity Active avoidance Analgesia

BETA-ENDORPHIN is an endogenous opioid peptide with profound behavioral effects in animals after intracerebroventricular (ICV) administration [2,9]. Since this route cannot be used in humans, it is important to determine whether beta-endorphin is behaviorally active after systemic administration. There are several reports in the literature that beta-endorphin causes analgesia in mice (8–28 mg/kg) [6, 8, 11] and cats (200 μg/kg) [5] after intravenous (IV) administration, plus a report that D-ala-2-beta-endorphin is behaviorally active after intraperitoneal administration in goldfish [10]. de Wied *et al.* [4] recently reported that subcutaneous beta-endorphin (0.1–1 μg) delayed extinction of pole-jumping avoidance behavior in rats. However, Bloom *et al.* [2] found that IV beta-endorphin produced no gross behavioral effects in rats at doses up to 1 mg/kg. We report here evidence that beta-endorphin influences operant conditioned behavior in rats after chronic IV administration, under conditions where there is no analgesic effect.

METHOD

Animals were 14 male Sprague-Dawley rats (200–220 g) included in a toxicology study which involved receiving 14 daily IV injections (via lateral tail vein) of either saline (0.35 ml) or synthetic human beta-endorphin (2.5 mg/kg). The human beta-endorphin was synthesized as previously described [8], suspended in saline (0.35–0.40 ml), and injected over 20 sec under blind conditions. Fifteen to 180 min after the eleventh injection, each animal received one-way active avoidance training to a criterion of 6 consecutive avoidance responses. The apparatus was a 122 cm-long runway, with conditional stimulus a 10 sec tone, unconditioned stimulus 0.5 mA footshock, and the intertrial interval 20 sec. Fifteen to 120 min after the twelfth and thirteenth injections, each animal was tested for analgesia using, respectively, the tail-flick method of D'Amour and Smith [3] and the hot-plate method of Ankier [1]. Saline and beta-endorphin groups were compared using the two-tailed Mann-Whitney U test.

RESULTS

One animal in each group showed intractable freezing responses during avoidance training, and was discarded from that part of the study. All other animals achieved the avoidance criterion within 38 trials. Beta-endorphin had no effect on the number of trials needed to achieve criterion, but did significantly lengthen response latencies (median of 8.6 sec versus 7.3 sec for saline group; $p<0.025$). Inspection of the data revealed no decrease in beta-endorphin effect with lengthening injection-test intervals (Table 1). There was no significant beta-endorphin effect on avoidance latencies or escape latencies when these were analyzed separately. Beta-endorphin had no analgesic effect in either the tail-flick or hot-plate procedures.

DISCUSSION

These results show that beta-endorphin is behaviorally active in rats after chronic IV administration and suggest that this effect lasts for at least 3 hr. The absence of any analgesic effect under these conditions suggests that: (1) operant conditioned behavior is more sensitive to influence by beta-

TABLE 1

EFFECT OF BETA-ENDORPHIN (2.5 MG/KG IV) ON RESPONSE LATENCIES IN ACTIVE AVOIDANCE TASK

Rat No.	Injection	Latency (sec)	Rat No.	Injection	Latency
1	endorphin	8.35	8	endorphin	(discarded)
2	saline	6.0	9	endorphin	8.30
3	saline	8.67	10	saline	8.13
4	saline	7.66	11	saline	(discarded)
5	endorphin	7.67	12	endorphin	12.2
6	endorphin	8.86	13	endorphin	9.18
7	saline	6.79	14	saline	6.99

endorphin than is nociception, or (2) there is no tolerance to effects on operant behavior, while there is to analgesia. The first possibility is supported by the recent finding that alpha-endorphin affects pole-jumping avoidance behavior in rats at doses (0.1–0.3 μg SC) which have little or no analgesic effect [4].

With regard to the second possibility, there is contradictory data in the literature. Bloom *et al.* [2] found no tolerance to the analgesic or catatonic effects of beta-endorphin in rats after seven daily injections (45 μg intracisternally), while Tseng *et al.* [12] found tolerance to both effects after seven injections (5–19 μg ICV). In cats, Hosobuchi *et al.* [7] found acute tolerance after one dose (25 μg ICV) to the analgesic effect of beta-endorphin, but none to the other behavioral effects (e.g., mild excitation).

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