Morphine Enhances Lateral Hypothalamic Self-Stimulation in the Rat[1] (36549)

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It has been reported that morphine inhibits self-stimulation behavior in the rat up to 1 hr after injection (1, 2). The effect of repeated morphine administration on self-stimulation, however, has not been examined. Since tolerance is developed to the narcotic and analgesic effects of morphine after repeated administration, it was our objective to determine whether the depressant effect of morphine on self-stimulation likewise would attenuate.

Method. Bipolar 30 gauge tungsten electrodes insulated with Epoxylite except at the cross sections of their tips were implanted stereotactically in 14 albino rats weighing between 240–400 g. Histological analysis at the end of the experiment revealed that all electrodes were localized in the lateral hypothalamic portion of the medial forebrain bundle at the level of the ventromedial hypothalamic nucleus. All surgical and histological procedures employed have been described elsewhere (3).

Seven to 10 days postoperatively the rats were trained to press a lever for a 0.2 sec train of bidirectional square waves (0.1 msec pulse duration; 100 pulse-pairs/sec) delivered by a Grass S8 stimulator through two stimulus isolation units. Peak-to-peak current intensity was monitored on a Tektronix RM 503 oscilloscope as the voltage drop across a 100 ohm resistor. A detailed description of the behavioral apparatus and programming equipment has been published (3).

The animals were run 10 min/day for 4–5 days at an optimal current value. During the next 6–9 days thresholds were determined by decreasing the current level 80 μA/day. Threshold was arbitrarily defined as the μA which yielded a maximum of 200 responses/10 min for 2 consecutive days. During the remainder of the experiment the animals were run daily with the current set 80 μA above threshold. Current values employed ranged between 320–800 μA.

Following a 6–7 day stabilization period at this current level, the rats were divided into two groups matched for their lever pressing rates. During the last 5 days of the experiment one group received daily injection of normal saline (1 ml/kg, subcutaneously); the other group was given daily injection of morphine sulfate (10 mg/kg, subcutaneously, calculated as the base).

On each of these 5 days the animals received a 10 min control period followed immediately by injection of the assigned agent. Each animal then was tested for a period of 10 min at hourly intervals for 6 consecutive hours. Prior to each of these sessions the animals were permitted 30 sec in order to begin self-stimulating. If an animal failed to initiate responding within this time, the experimenter administered priming stimulation for 1 min. Then, whether the rat was responding or not, the number of lever presses was recorded for the next 10 min.

Results. As shown in Fig. 1, morphine significantly reduced responding for 2 hr following injection on Day 1. A significant increase in responding, however, was seen 5–6 hr after injection.

Complete tolerance to the suppressive influence of morphine was developed by Day 3 (Fig. 1). In contrast, the excitatory action of morphine continued throughout the 5 day testing period. In fact, this excitatory effect

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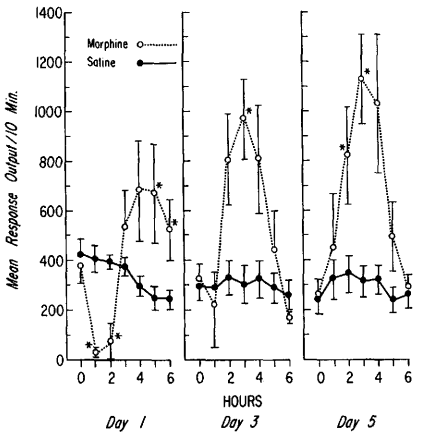

FIG. 1. Mean number of lever presses per 10 min for rewarding hypothalamic stimulation during the control (0) periods and for each hour after injection of morphine (10 mg/kg, sc) or saline (1 ml/kg, sc) on days 1, 3, and 5. Vertical bars represent the standard errors of the means. Asterisks indicate significant ($p < .05$) group differences as determined by the Mann-Whitney U test, two-tailed. There were seven animals in each group.

of morphine tended to be enhanced and was apparent earlier after repeated morphine injection.

One hour following morphine injection on Day 1, all rats demonstrated muscular rigidity, exophthalmos, a mild piloerection, and slowing of respiratory rate (three animals were cyanotic). These symptoms of morphinization were not seen 4 hr postadministration. After repeated injection such toxic effects for the most part were absent. In addition, at the end of the experiment, the two groups did not show any significant differences in body weight.

Discussion. It is apparent that morphine has both an inhibitory and excitatory effect on self-stimulation behavior. It is clear, furthermore, that in contrast to the excitatory effect, complete tolerance is developed to the suppressive effect. Moreover, the fact that tolerance does develop to the suppressive effect demonstrates that the excitatory action is not due to a rebound phenomenon.

Whether these effects on rewarding hypothalamic stimulation are due to a direct or indirect action of morphine on the excitability of the medial forebrain bundle system is a matter for conjecture. It is nonetheless tempting to speculate that these changes in excitability, expressed as increased self-stimulation rates, could be useful as a model for studying the euphorigenic property of morphine.

Summary. Morphine sulfate (10 mg/kg, subcutaneously) suppressed self-stimulation 1–2 hr after injection but augmented it 5–6 hr postadministration. Complete tolerance to the depressant effect was developed after three daily injections. The excitatory effect, however, tended to increase throughout the 5 day testing period.

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