Changes in Self-Stimulation Response during Chronic Morphine Treatment and after Withdrawal of Morphine in Rats

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ABSTRACT—Morphine (5–20 mg/kg, s.c.) dose-dependently inhibited the hypothalamic self-stimulation response 1–2 hr after administration of the drug. Thereafter, slight increase in the self-stimulation response was seen 4–8 hr after drug administration. The depressant effect induced by 10 mg/kg, s.c. of morphine on the self-stimulation response was antagonized by 1 mg/kg, s.c. of levallorphan. Repeated administration of morphine (10 mg/kg, s.c.) resulted in an increase of the self-stimulation response. The self-stimulation response rate was increased significantly 24 and 48 hr after withdrawal of morphine in chronic-morphine-treated rats; In these rats, the initial dose of morphine (10 mg/kg, injected s.c. twice daily 7 days a week) was increased gradually until at the end of 5 weeks, each dose was 50 mg/kg, s.c.

Keywords: Self-stimulation, Morphine, Withdrawal sign

In the self-stimulation study, the animal presses the lever without ceasing to receive the electrical stimulation in the rewarding area of the brain (1). The lever pressing response in self-stimulation seems to be quite similar to the behavior in which the animal desires to continue opiate administration. On the other hand, it has been reported that the self-stimulation response is initially depressed by doses of morphine above 5.0 mg/kg (2), after which a delayed rebound increase in response may follow (3).

The purpose of this study was to examine the changes in self-stimulation response after withdrawal of drugs in morphine-dependent rats. The effects of single and repeated administrations of morphine on hypothalamic self-stimulation were also investigated.

The subjects were male Wistar HLA strain rats weighing 250–300 g. The animals were housed individually in a room illuminated from 8:00 A.M. to 6:00 P.M. Room temperature was maintained at $23 \pm 1^\circ\text{C}$ with $65 \pm 5\%$ relative humidity. Food and water were available ad libitum. The procedure of surgery was as follows: Bipolar stainless steel electrodes (200 μm in diameter, tip distance of 0.5–0.8 mm) were implanted stereotactically in the posterolateral hypothalamus under pentobarbital anesthesia. The coordinates were 0.5 mm posterior to the bregma, 1.8 mm lateral to the midline and 8.0 mm deep from the surface of the cortex, according to the atlas of de Groot (4). The experimental chamber was a modified Skinner box. The side and front walls (containing a door)

were composed of clear plexiglas, while the remaining walls were constructed of white plexiglas. The floor was covered with a black rubber plate. A stainless steel lever (2.5-cm-thick and 6.5-cm-wide) protruded 2.5 cm through the right wall and a red lamp was placed just above the lever. A train of 60-Hz sinusoidal waves of 20–50 μA was delivered for 0.25 sec with each lever pressing. The drugs used were morphine hydrochloride (Dainippon, Osaka) and levallorphan tartrate (Takeda, Osaka), all of which were administered s.c. In the tests of single and repeated administrations of morphine, the rats that showed a constant lever pressing response of 60–100/min at 50 μA were selected for the drug test. Eight rats were used for each group. In the withdrawal test, 24 rats were used, and they were divided into 3 groups: low (10–20 responses/min at 20 μA), median (30–50 responses/min at 30 μA) and high (80–100 responses/min at 50 μA) rate response groups.

One-way analysis of variance with Dunnett's test was used to determine statistical significance.

Morphine dose-dependently inhibited the hypothalamic self-stimulation response. At a dose of 5 mg/kg, the drug elicited a significant depression 1 hr after administration. At doses of 10 and 20 mg/kg, a significant inhibition was observed 1 and 2 hr after drug administration, respectively. At 4–8 hr after morphine administration, the drug caused an increase of response in all doses used, but no significant effect was observed (Fig. 1A). The inhibitory

Fig. 1. Effects of single and repeated administrations of morphine on hypothalamic self-stimulation behavior. A: Single administration. ○, saline; ●, 5 mg/kg; △, 10 mg/kg; ▲, 20 mg/kg. B: Repeated administration. ○, saline; ●, Day 1; △, Day 3; ▲, Day 7; □, Day 10. *,: Significantly different from the saline-treated control group with $P < 0.05$ and $P < 0.01$, respectively.

effect induced by 10 mg/kg of morphine on this response was antagonized entirely by pretreatment with 1 mg/kg of levallorphan, and a significant effect was observed 1 and 2 hr after drug administration in the morphine-alone-treated group. In the repeated administration study, morphine was injected at a dose of 10 mg/kg for 10 days. On the 1st day, the self-stimulation response was decreased significantly 1 and 2 hr after drug administration. On the 3rd day, the inhibition of self-stimulation was attenuated; and on the 7 and 10th days, the depressant effect of morphine on this response was abolished, and a significant facilitatory effect appeared 2 and 4 hr after morphine treatment (Fig. 1B). In the morphine withdrawal test, rats were made tolerant to morphine in the following manner: the initial dose of morphine (10 mg/kg, injected s.c. twice daily 7 days a week) was increased gradually until at the end of 5 weeks, each dose was 50 mg/kg, administered as described above. During morphine treatment, the self-stimulation response was tested 12 hr after administration of morphine on days 7, 14, 21, 28 and 35. On day 36, a withdrawal state was induced by withdrawing morphine. As shown in Fig. 2A, the self-stimulation response was not changed during morphine treatment in all groups. However, the self-stimulation response was significantly increased 24 and 48 hr after withdrawal of morphine. In addition, 2 hr after administration of morphine (10 mg/kg, s.c.), the increase in self-stimulation response was abolished (Fig. 2B).

In this study, it was found that morphine showed both inhibitory and excitatory effects on the self-stimulation response, and development of tolerance to the suppressive effect was also observed. These results were essentially in accord with observations by Adams et al. (3). However, the facilitatory effect by single administration of morphine was somewhat weak compared with the finding of Adams et al. (3). It is well known that there are good correlations between the self-stimulation response and brain catecholamine levels. For instance, amphetamine increased the self-stimulation response and reserpine decreased the self-stimulation response (5, 6). On the other hand, Akera and Brody (7) reported that brain noradrenaline level was increased during chronic morphine treatment.

Interestingly, it was also found that the self-stimulation response was increased significantly 24 and 48 hr after withdrawal of morphine. At the same times, withdrawal signs such as decrease of body weight, diarrhea, piloerection and wet dog behavior were also detected. It is well known that withdrawal signs by natural withdrawal of morphine peaked 24–48 hr after withdrawal of morphine. Therefore, it seems likely that the increase in response rate after withdrawal of narcotics was a result of the withdrawal state. As shown in Fig. 2B, the effects observed in the low and median response groups were more obvious than that seen in the high response group. The high response group showed less effect than the other two

Fig. 2. Changes in self-stimulation response during chronic administration of morphine and after withdrawal of morphine. A: Chronic administration. ○, 20 μ A; ●, 30 μ A; △, 50 μ A. Self-stimulation response was tested 12 hr after administration of morphine on days 7, 14, 21, 28 and 35. B: After withdrawal of morphine. ○, 20 μ A; ●, 30 μ A; △, 50 μ A. Self-stimulation response was tested 6, 12, 24 and 48 hr after morphine (50 mg/kg) treatment. *, **, Significantly different from the values at 6 hr after administration of 50 mg/kg of morphine with $P < 0.05$ and $P < 0.01$, respectively.

groups because the self-stimulation rate in this group had already reached its maximum. In the interaction between withdrawal signs and brain catecholamine level, Gunne (8) described that noradrenaline level of the brain was significantly decreased during the withdrawal period. Akera and Brody (7), on the contrary, described that there is no relationship between the addiction cycle and the levels of brain catecholamines. Sloan et al. (9) also reported that the brain noradrenaline level was not changed after withdrawal of morphine. Therefore, monitoring the brain catecholamine level may not be a good parameter for determining the increase in self-stimulation response after withdrawal of morphine. On the other hand, Babbini et al. (10) reported in a fixed-interval schedule experiment that an increase in lever pressing was exhibited by withdrawal of morphine. Collins and Weeks (11) also reported that continuous intravenous infusion of morphine decreases and nalorphine increases the voluntary morphine intake in dependent rats maintained with 10 mg/kg of morphine on a fixed-ratio reinforcement schedule of 10 (FR-10). From these findings, an increase in self-stimulation response observed after withdrawal of morphine seems to suggest that the electrical stimulation of the reward area has the same effect as the morphine intake.

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