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Chronic Morphine Fails to Enhance the Reward Value of Prefrontal Cortex Self-Stimulation

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CORBETT, D. *Chronic morphine fails to enhance the reward value of prefrontal cortex self-stimulation.* PHARMACOL BIOCHEM BEHAV **42**(3) 451–455, 1992.—Dopamine (DA) plays an important role in the rewarding effects of drugs of abuse and intracranial self-stimulation (ICSS). We previously reported that ICSS derived from the prefrontal cortex appears insensitive to the reward-enhancing effects of amphetamine, a drug that increases DA release and reward at other ICSS sites. In the present study, rats with prefrontal electrodes were tested to see if morphine (7.5 or 10.0 mg/kg, IP) given once per day for 10 days enhanced prefrontal reward as assessed with the curve-shift method. Morphine initially produced sedation; however, after 3–4 days response rates increased sharply while frequency thresholds were unaffected. These results demonstrate that morphine does not enhance prefrontal ICSS reward and provide further evidence that prefrontal brain stimulation reward does not display the same characteristics as other ICSS sites.

Self-stimulation Morphine Prefrontal cortex Dopamine

SELF-STIMULATION at medial forebrain bundle (MFB) sites and drugs of abuse (e.g., stimulants and opiates) are thought to produce their rewarding effects by an action on the mesolimbic/mesocortical dopamine (DA) neurons located in the ventral tegmental area (VTA) (2,13,35,36). Animals will readily self-administer brief trains of electrical stimulation or drugs of abuse to this brain region (3,9,23). Moreover, neurotoxic lesions or pharmacological inactivation of the DA systems interferes in a fairly selective manner with intracranial self-stimulation (ICSS) (14,23,30,31) and intravenous self-administration of stimulant (19,24,37) and opiate drugs [(35), but see (22)]. While the DA hypothesis of reward is quite compelling, there are some findings that do not easily fit within this conceptual framework. For example, ICSS sites in the medial prefrontal cortex (MFC) are relatively insensitive to lesions of the DA pathways (6,23,28) and the threshold-lowering effects of amphetamine (29). Recently it has been shown that MFB ICSS is more sensitive to the reward-degrading effects of neuroleptic drugs than is prefrontal ICSS (5).

However, some drugs of abuse have been reported to enhance the reward value of MFC ICSS. Using rate measures, Lorens (18) noted large increases in responding for MFC ICSS. Since morphine has also been found to enhance rates and lower the threshold for MFB ICSS (11,12,16,25) it was decided to examine the effects of low doses of morphine on MFC ICSS. This experiment utilized a shift-curve method that has been employed to separate drug-induced reward effects from drug-induced effects on performance (e.g., sensorimotor function) (10,32).

METHOD

Subjects and Procedure

Male Sprague-Dawley rats were implanted with monopolar electrodes aimed at the MFC under sodium pentobarbital anesthesia. Following recovery, they were trained to lever press for 500-ms trains of 0.1-ms pulses delivered at 100 Hz. During training, the current intensities were held constant at 400 μA for each animal. After 10–14 days of lever press training, rats were trained on a rate-frequency (curve-shift) paradigm where the frequency was lowered in 0.1 log unit steps until the animal ceased to respond. Each frequency was available for 1 min; then, the lever retracted for 5 s., a free or priming stimulation at the next frequency value (i.e., 0.1 log unit lower) was delivered, and the lever extended. This sequence was repeated until the lowest frequency value was attained. In the present experiment, each rat was tested at 6 or 7 frequencies ranging from 16–79 Hz. Four rate-frequency sweeps were conducted each day. Currents were adjusted individually (mean = 226.4 μA ± 55.38 SD) to yield reliable responding.

Reward and Performance Measures

All stimulation parameters were delivered and controlled by a microcomputer-based brain stimulation unit (4). The fre-

quency that generated half-maximal (half-max) responding was calculated for each rate-frequency trial. This value is also referred to as the locus of rise and has been found to be sensitive to manipulations that degrade the effectiveness or reward value of the brain stimulation (10). For example, decreasing current intensity or administering drugs that reduce reward (e.g., neuroleptics) causes the rate-frequency curve to shift to the right and the half-max increases. Conversely, if current is increased or reward-enhancing drugs are given, the curve will shift to the left and the half-max will decrease (10,32).

Drugs and Testing Procedure

Rats were tested on the rate-frequency schedule until the half-max values varied less than 0.1 log unit over 3 consecutive test days and response rates were no longer increasing. It required approximately 3 weeks of rate-frequency testing for animals to reach this stability criterion.

Once stability had been achieved, rats were injected (IP) with either 7.5 (n = 7) or 10.0 mg/kg (n = 7) morphine. Pilot data indicated that doses up to 5.0 mg/kg morphine had little or no effect on MFC ICSS. Animals were tested 1 and 3h after drug injection. This procedure was repeated for 10 consecutive days. After the 10th day of testing, the drug-free rats were tested once per day for 1 or 2 days to see if response rates and half-max measures had returned to baseline values.

Histology

At the end of behavioral testing, animals were killed with an overdose of sodium pentobarbital and perfused with physiological saline followed by 10% phosphate-buffered formalin. Brains were stored in the same fixative for a minimum of 3 days prior to being transferred to a 30% sucrose-formalin solution for 2 additional days. Brains were frozen using isopentane cooled with liquid nitrogen. Frozen, 40-μm sections were cut, stained with cresyl violet, and electrode locations determined.

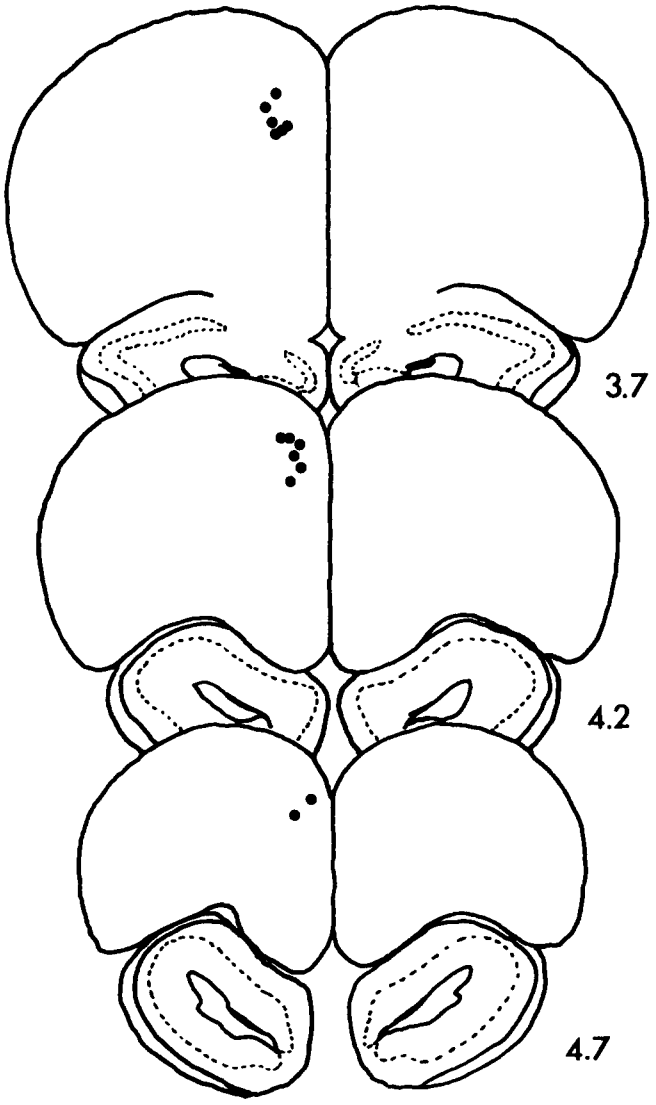

FIG. 1. Schematic representation of ICSS electrode sites localized to the MFC.

RESULTS

All electrode placements (Fig. 1) were found to be located within the medial aspect of the anterior prefrontal cortex, that is, the prelimbic area (1).

Initially, both doses of morphine produced sedation that interfered with animals' ability to respond and prevented meaningful calculation of half-max and response measures. This was particularly evident at the 1-h test on the first drug day (Table 1). Three hours after injection, most rats had recovered from the sedative effects and half-max values could be determined. Over test days, the sedative effects of morphine abated so that by the 5th day of testing nearly all animals were responding normally 1 h after drug injection.

The half-max measures were unaffected by the morphine injections, never changing more that 5% from premorphine levels. However, response rates increased sharply over test days by 40–50% in animals tested 3 h after injection of either 7.5 or 10.0 mg/kg morphine (Table 1). Representative rate-frequency curves from two animals are shown in Fig. 2. Tests conducted after morphine had been discontinued revealed that while half-max values were at baseline levels response rates remained elevated by approximately 20–25% compared to predrug values.

DISCUSSION

Morphine at either 7.5 or 10.0 mg/kg failed to lower half-max measures although response rates increased substantially and tended to persist above baseline levels, even when morphine was discontinued after 10 consecutive days of drug administration. The usual interpretation given such data would be that morphine increased the performance capability of animals either by enhancing motor output directly or perhaps by decreasing factors that interfere with responding for MFC ICSS. For example, MFC stimulation produces motoric inhibition, an effect that would limit response rates and that has been suggested to be partly responsible for the slow acquisition of MFC ICSS (7,8). The persistent elevation of response rates observed after morphine was discontinued may represent a form of behavioral sensitization like the sensitization of

TABLE 1

EFFECTS OF CHRONIC MORPHINE (7.5 AND 10 mg/kg) ON MFC HALF-MAX AND RESPONSE RATE (R) MEASURES RECORDED 1 OR 3 h AFTER INJECTION

	Day 1	Day 5	Day 10
Morphine 7.5 mg/kg			
Half-max$_1$	6/7 U	+1.65% ± 6.14 (6)	+1.05% ± 4.23 (7)
Half-max$_3$	−1.11% ± 5.00 (7)	−0.56% ± 4.27 (6)	+0.59% ± 2.55 (7)
R_1	6/7 U	+1.07% ± 17.98 (6)	+4.62% ± 36.70 (7)
R_3	−6.49% ± 10.26 (7)	+40.2% ± 21.5 (6)	+50.9% ± 29.10 (7)
Morphine 10 mg/kg			
Half-max$_1$	5/7 U	+4.3% ± 3.78 (5)	+4.13% ± 3.97 (5)
Half-max$_3$	−1.9% ± 1.66 (6)	+0.81% ± 3.33 (7)	+0.74% ± 3.08 (7)
R_1	5/7 U	+22.9% ± 5.12 (5)	+25.9% ± 13.9 (5)
R_3	+12.5% ± 5.9 (6)	+25.4% ± 18.23 (7)	+43.9% ± 32.17 (7)

U, undefined (no half-max or R measures could be calculated). Numbers in parentheses refer to the number of animals.

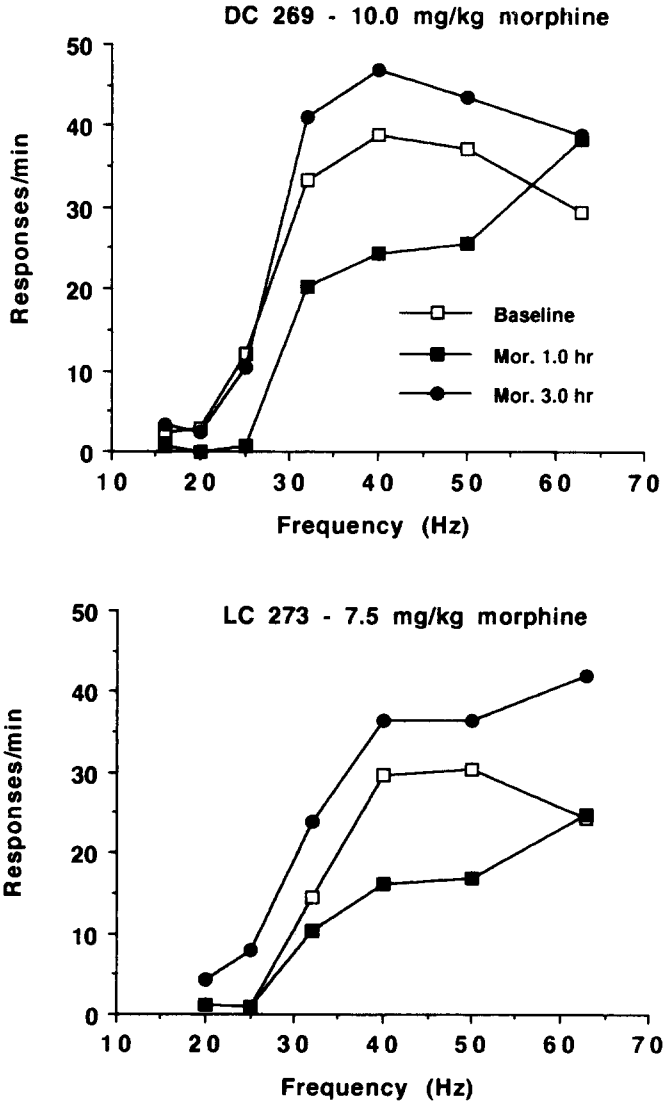

FIG. 2. Representative rate-frequency curves from two rats injected with 7.5 mg/kg and 10.0 mg/kg morphine. Data were recorded on the fifth day of morphine treatment. Each point is the average of four rate-frequency runs.

locomotor activity observed after chronic morphine administration (15).

Previous reports have shown that chronic morphine lowers the threshold and increases responding for MFB ICSS (11,20,26,33), especially after animals have become tolerant to the initial sedative effects of the drug. There have been relatively few studies that have examined the effects of morphine on ICSS loci that lie distal to the MFB–VTA neuroaxis. Lorens (18) found evidence for increased responding at electrodes within the MFC while Leibman and Segal (17) found sites close to the substantia nigra where morphine had no effect or decreased responding. Interestingly, responding at more dorsal ICSS sites was increased by morphine pretreatment. The fact that morphine did not lower half-max measures suggests that the facilitation of prefrontal ICSS observed by Lorens was a performance effect.

Previous studies (5,29) from this laboratory have shown that MFC ICSS is relatively insensitive to amphetamine and DA antagonists, drugs that, respectively, would be expected to enhance and reduce brain stimulation reward. If morphine produces its rewarding effects via an action on VTA DA neurons, as has been advocated by Wise and colleagues (34–36), it would follow that morphine would not enhance the reward value of MFC ICSS since this site appears not to involve the DA systems.

The observation that some ICSS sites in the substantia nigra are not facilitated by morphine (17) is noteworthy in view of the present results and also with respect to a previous study showing that substantia nigra (but not MFB) ICSS was attenuated by prefrontal lesions (27). This latter finding together with the morphine data suggest that the prefrontal cortex and substantia nigra may represent a reinforcement system that is largely independent from the DA-modulated MFB–VTA system. However, a recent study has noted that cocaine, a DA uptake inhibitor, lowered train duration thresholds of MFC ICSS (21). This result is difficult to reconcile with the present data and with earlier data demonstrating that amphetamine failed to lower MFC frequency thresholds (29). Cocaine, amphetamine, and morphine all functionally augment DA synaptic transmission, albeit via different mechanisms, so all of these drugs should have more or less similar effects on MFC ICSS. It may be that cocaine's facilitatory effects on MFC ICSS are not mediated by an action on mesolimbic/mesocortical DA systems but by some other neurochemical process. The precise role of the prefrontal cortex in cocaine reinforcement and reinforcement in general remains an intriguing and important question.

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