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Chronic Naltrexone Treatment Increases The Heroin-Produced Facilitation of Self-Stimulation

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SCHENK, S. AND E. NAWIESNIAK. *Chronic naltrexone treatment increases the heroin-produced facilitation of self-stimulation.* PHARMACOL BIOCHEM BEHAV 22(2) 175–177, 1985.—The facilitatory effects of heroin HCl (0.25 mg/kg, SC) on self-stimulation (SS) of the lateral hypothalamus before and after chronic treatment of naltrexone (10 mg/kg, SC, for 20 days) or vehicle were compared. The group that received chronic naltrexone had a larger heroin-induced facilitation of SS than the group that received vehicle. These data suggest that the sensitivity to the facilitatory effect of heroin on SS may be related to the amount of opiate receptor binding which is increased following chronic antagonist treatment. However, neither acute nor chronic treatment with naltrexone produced any significant changes in SS thresholds, suggesting that the directly stimulated substrate for the rewarding effect of brain stimulation is unlikely to be endorphinergic but is apparently modulated by the endogenous opioid system.

Heroin Naltrexone Self-stimulation

OPIATES exert facilitatory effects on self-stimulation (SS) which are highly variable [12]. These effects are often preceded temporally by a suppression that shows tolerance with repeated injections [5,6]. It is believed that these two phases of opiate action on SS reflect the activation of distinct neural substrates; the enhancement of SS may well reflect activation of neurons subserving the rewarding effects of this class of abused drug [4,6]. Indeed it has been suggested that opiates exert their rewarding effects via activation of a specific subset of the elements within the SS substrate. It is possible that the across subject variance in the magnitude and duration of the facilitatory effect reflects, at least in part, the individual's sensitivity to the drug's reinforcing effect. One factor that may contribute to the individual response configuration is the amount of central opiate receptor binding.

Chronic treatment with the opiate antagonists, naloxone [9] or naltrexone [16], increases opiate binding and increases the analgesic potency of morphine [15] and stress [2] in rats. If the magnitude of the opiate-produced facilitation of SS is similarly related to the degree of opiate receptor binding, then supersensitivity induced by chronic treatment with the long acting opiate antagonist, naltrexone [16], may be expected to result in an enhancement of a subject's responsiveness to opiates.

METHOD

Subjects

Subjects were 26 male Sprague Dawley rats (Canadian Breeding Farms Ltd., St. Constant, Quebec) weighing 350–450 grams at the time of surgery. The subjects were anesthetized with sodium pentobarbital (60 mg/kg) and stereotaxically implanted with stainless steel (0.25 μm) stimulating electrodes insulated with Formvar except for the cross-section of the tip. They were aimed at the lateral hypothalamus (LH) (incisor bar at +5.0 mm relative to the interaural line; 0.4 mm caudal to bregma; 1.4 mm lateral to the saggital suture; 8.0 mm ventral to dura).

Apparatus

All testing was carried out in a wooden box with a Plexiglas front (25×25×82 cm). Depression of a lever (Lehigh Valley Electronics, 101–05) triggered a 500 msec train of cathodal rectangular pulses, 0.1 msec in duration. Stimulation parameters were controlled by integrated circuit pulse generators and constant current amplifiers [10].

Procedure

Approximately 1 week following surgery, the rats were trained to self-stimulate. The current intenstiy and frequency were manipulated so that a maximal rate of responding was attained. Once responding was at a high rate (>40 responses per minute) the current intensity was fixed and performance was stabilized by determining the frequency required to produce a half maximal rate of responding. These required frequencies were determined at 20 minute intervals over a 3 hour period each day. In these tests, the pulse frequency was decreased every minute in 0.1 log steps from the value that

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produced a maximal rate of responding to that at which the rat failed to respond. The stimulation frequency that supported a half maximal rate of responding was defined as the required frequency and was determined by graphical interpolation. When the difference between any two required frequency measures on a given test day did not exceed 0.1 log units, the rat's behavior was considered stable and the experiment proper began. Seven days of training were usually sufficient for the rats to meet this criterion for stability.

The experiment proper consisted of 3 phases: (1) pre-treatment heroin test; (2) chronic treatment with naltrexone or Ringer's solution (20 days); and (3) post treatment heroin test.

(1) Pre-treatment heroin test. On day 1, subjects were administered an injection of Ringer's solution (1 ml/kg, SC) and required frequencies were determined pre-injection and at 20 minute intervals for 2 hours post-injection. The range of required frequencies for all subjects met the criterion for stability as described above. On day 4, the animals were injected with Heroin HCl (250 μg/kg, SC) and the effects of the drug were assessed in the same manner as on the Ringer's control day. The peak decrease in required frequency was determined for each rat by compring pre- and post-injection data for the test day. The subjects were then distributed into treatment groups so that the average peak facilitation was matched for the two groups (see Table 1).

(2) Chronic treatment. During this phase of the experiment, the animals received daily injections of either naltrexone HCl (10 mg/kg, SC, n=16) or Ringer's solution (1 ml/kg, SC, n=10) for 20 days. In order to assess both the acute and chronic effects of naltrexone on SS, required frequencies were determined for each group on days 1, 6, 13 and 19 of treatment. Tests were conducted pre-treatment and at 20 minute intervals for 1 hour post-injection.

(3) Post-treatment heroin test. Following chronic treatment, the effects of heroin on SS were again assessed in exactly the same manner as described for phase 1 of the experiment. The rats were tested 2 and 5 days following the last of the chronic injections. The peak facilitation produced by heroin was compared to the peak facilitation obtained in phase 1 and the difference in these values for each rat served as the dependent measure.

At the completion of the experiment, the rats were injected with a lethal dose of sodium pentobarbital and perfused intracardially with 0.9% saline solution followed by 10% formalin. The brains were removed, frozen and sliced in 40 μm sections. All electrode tips were located in the lateral hypothalamus [11].

RESULTS

Table 1 shows the mean peak facilitation of SS (log units) following heroin injections in the pre-treatment and post-treatment phases. The average peak facilitation for both the Ringer's and the naltrexone groups is approximately the same before treatment. The magnitude of the heroin produced facilitation of SS tended to decrease following chronic Ringer's treatment and increased slightly in the group that received chronic injections of naltrexone.

A 2-way ANOVA (Treatment × Days) with repeated measures over the days factor was performed on the post-treatment data. The group that received chronic naltrexone had a greater heroin-produced facilitation of SS than the group that received chronic injections of vehicle, $F(1,23)=4.09$, $p=0.05$.

TABLE 1

PEAK FACILITATION (LOG UNITS) ±S.E.M. PRODUCED BY HEROIN (0.25 mg/kg) BEFORE AND AFTER 20 DAYS OF DAILY INJECTIONS OF EITHER NALTREXONE (10 mg/kg) OR RINGER'S SOLUTION

	Pre-treatment	Post-treatment*	
		2 days	5 days
Ringer's (n=10)	0.068 ± 0.019	0.052 ± 0.016	0.036 ± 0.017
Naltrexone (n=16)	0.058 ± 0.013	0.073 ± 0.012	0.085 ± 0.019

*$p=0.05$ between groups.

We were also interested in assessing the acute and chronic effects of naltrexone on SS. The acute effects were determined by comparing the peak increase in required frequency following injection of naltrexone or Ringer's on day 1 during chronic treatment to the pre-injection baseline on that day (Table 2). The naltrexone group tended to show a greater increase in required frequency (i.e. suppression of behavior) than the Ringer's group although the difference was non-significant, $t(23)=1.57$, $p>0.05$.

To assess the chronic naltrexone effects, the pre-injection required frequencies on days 7, 13 and 19 during chronic treatment and days 2 and 5 following the treatment were compared to the baseline required frequencies for the first heroin test day. This allowed us to observe whether or not SS thresholds had changed from the beginning of the experiment to the end as a result of long-term treatment with the opiate antagonist. Again, the required frequencies tended to be higher during chronic treatment than when the experiment began (Table 2) although the shifts in required frequency were approximately equal for both the Ringer's and naltrexone groups (student t's, N.S.).

DISCUSSION

Rats treated chronically with Ringer's solution were less sensitive to heroin than rats chronically treated with the opiate antagonist, naltrexone. The magnitude of the increase in the naltrexone-treated group was not large (0.027 log units compared to pre-treatment heroin facilitation, day 5 post treatment) but when combined with the decreased sensitivity in the Ringer's group (−0.032 log units on day 5 post-treatment) the difference between groups was significant.

One possible explanation for the decrease in sensitivity of the Ringer's group is related to the housing condition of the rats during the 35 day experimental procedure. Isolation housing decreases the behavioral efficacy of opiates in a variety of tests [1, 8, 14]. It has been suggested that this housing manipulation can produce alterations in a subject's sensitivity to opiates by altering opiate receptor binding [14,15]. That this manipulation decreases opiate receptor binding [13] and that chronic opiate antagonist treatment increases opiate receptor binding [16] further suggests that the effects of these two manipulations on behavior should be antagonistic. Therefore, it may not be surprising that the Ringer's group showed a decreased sensitivity over the

TABLE 2

CHANGES IN SS THRESHOLD (LOG UNITS) FOR RATS RECEIVING RINGER'S OR NALTREXONE TREATMENT

Acute	Chronic				
	During treatment			Post-treatment	
Day 1	Day 7	Day 13	Day 19	Day 2	Day 5
Ringers					
0.014 ± 0.011	0.020 ± 0.019	0.019 ± 0.030	0.029 ± 0.022	0.015 ± 0.024	−0.006 ± 0.018
Naltrexone					
0.042 ± 0.014	0.027 ± 0.012	0.025 ± 0.016	0.039 ± 0.016	0.043 ± 0.019	0.031 ± 0.020

Acute effects were determined by comparing the pre- and post-treatment threshold on the first day of chronic treatment. Chronic effects were assessed by comparing pre-injection baseline thresholds on Days 7, 13 and 19 during treatment and on days 2 and 5 following treatment to the pre-injection threshold on the first heroin test day. Positive values indicate that the frequency threshold had increased.

course of the experiment with a corresponding increased sensitivity in the naltrexone treated rats.

Acute naltrexone was ineffective in altering the rewarding value of brain stimulation. Although opiate antagonists have been reported to decrease rates of responding for SS [33], the lack of an effect on SS thresholds [7] argues that the antagonist-induced suppression of rates is more likely related to a performance artifact which would more readily express itself when a response rate measure is used. We also failed to observe any effects of chronic naltrexone on SS. Taken together with the facilitation of SS produced by heroin, these findings suggest that the directly stimulated substrate for the rewarding effects produced by LH stimulation is not endorphinergic. Rather, the activity of the substrate can be modulated by an endogenous opioid system.

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