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Changes in Response Rates and Reinforcement Thresholds for Intracranial Self-Stimulation During Morphine Withdrawal

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SCHAEFER, G. J. AND R. P. MICHAEL. *Changes in response rates and reinforcement thresholds for intracranial self-stimulation during morphine withdrawal.* PHARMACOL BIOCHEM BEHAV **25**(6) 1263–1269, 1986.—Rats were implanted with stimulating electrodes in the medial forebrain bundle-lateral hypothalamus and were trained in an auto-titration brain self-stimulation paradigm. When response rates and reinforcement thresholds were stable, the animals were implanted with subcutaneous osmotic minipumps (Alzet, 2ML1) which continually delivered morphine (1.2 mg/kg/hr as the base, n=16) or saline (10.0 μl/hr, n=11). After one week the pumps were removed, and the animals were again tested in the auto-titration paradigm following the daily administration of either saline (spontaneous withdrawal) or 1.0 mg/kg naloxone (precipitated withdrawal). During the eight-day withdrawal phase there was a decrease in the rate of lever-pressing for the morphine dependent animals and this was greatest on the first day. The magnitude of the decrease was greater in the precipitated withdrawal group than in the spontaneous withdrawal group and an increase in the reinforcement threshold occurred only with precipitated withdrawal. Animals in both groups lost weight when measured each morning, but the precipitated group showed greater weight loss during the day. In addition, animals in the precipitated withdrawal group had diarrhea and showed a higher incidence of withdrawal signs than both the non-dependent (control) and spontaneous withdrawal groups. These experiments provide a detailed account of opiate withdrawal following the continuous subcutaneous infusion of a small dose of morphine for one week.

Morphine Naloxone Osmotic minipump Brain self-stimulation Response rate Reinforcement threshold Withdrawal

THE chronic administration of morphine almost invariably results in physical dependence. This can be demonstrated by measuring biochemical, physiological and behavioral changes after terminating drug administration, and they together constitute the abstinence syndrome [19,28]. There are numerous reports describing these changes, and among them are changes in operant behavior for food reinforcement [2]. Morphine also alters operant behavior that is reinforced by intracranial self-stimulation (ICSS) [7, 9, 12], and we have previously described changes in the rate of lever pressing for ICSS during withdrawal from a 4-day regimen of twice daily morphine injections [24]. In that study, the rate of lever-pressing was significantly decreased during the first day of withdrawal, and responding gradually returned to baseline values over the course of a week. The magnitude of the decrease was greater when the opiate antagonist, naloxone, was administered during the withdrawal phase. During withdrawal, all animals showed similar daily weight losses when compared with controls. In the present study, we wished to investigate if there were also changes in reinforcement thresholds for ICSS during withdrawal by utilizing the unique properties of ICSS reward. The effects of both spontaneous and naloxone-precipitated withdrawal on changes in the rate of responding and in the reinforcement threshold are described here. In addition, changes in body weight were measured in control and dependent animals, and the check list of Collier *et al.* [5] was used to assess the occurrence of other behavioral and physiological changes during the withdrawal phase.

Morphine dependence can be produced by multiple injections or continuous infusions [7, 9, 12, 24], but the use of multiple injections has been criticized [6] because the animals are exposed to high doses that wane over the course of several hours, only to be raised abruptly again by the next

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TABLE 1

NUMBER OF ANIMALS IN EACH GROUP SHOWING WITHDRAWAL SIGNS IN THE 95 MINUTES AFTER THE INJECTION OF SALINE OR NALOXONE

Group	Sign	N	Day			
			1	2	3	4
(1) Control	A. Diarrhea	11	0	0	0	0
	B. Irritability to touch or handling		0	0	0	0
	C. Body shakes		0	0	0	0
	D. Salivation		0	0	0	0
(2) Spontaneous Withdrawal (Saline)	A. Diarrhea	7	2	1	0	0
	B. Irritability to touch or handling		0	1	0	0
	C. Body shakes		1	0	0	0
	D. Salivation		0	0	0	0
(3) Precipitated Withdrawal (Naloxone)	A. Diarrhea	9	9	8	9	4
	B. Irritability to touch or handling		8	6	2	0
	C. Body shakes		7	1	0	0
	D. Salivation		8	1	0	0

See text for details on significance values

injection. There is, therefore, the possibility that animals actually experience withdrawal episodes during chronic drug administration. To preclude this, the animals in this study were implanted with osmotic minipumps containing either morphine or saline solution. This permitted animals to receive a constant infusion of morphine over the course of a week and allowed a more immediate termination of the drug effect.

METHOD

Animals

Twenty-seven adult male Sprague-Dawley rats (336–490 g) were used in this study. Between test sessions, animals were group housed (3–4 per cage) in a colony room with free access to food and water. The lights were on in the colony room between 07:00–19:00 hr, and the animals were tested during the lights-on phase.

Apparatus

Tests were conducted in an operant chamber (31×30×29 cm high) equipped with a conventional lever (G6312, Ralph Gerbrands Co., Arlington, MS) (stimulation lever), which was positioned 10 cm above a grid floor. An omnidirectional lever (G6313, Ralph Gerbrands Co.) (reset lever) was suspended from the ceiling near the opposite wall. The stimulating and titrating apparatus have been described in detail previously [22]. In this auto-titration experiment, each press on the stimulation lever produced a 100 msec train of biphasic pulses at 100 Hz; each pulse was 0.2 msec duration. After each 15th lever-press, the current was automatically decreased one step which equalled 5 μA; the current was held constant at each step. The starting current (range: 110–230 μA) for each animal was set at approximately 50 μA above threshold (10 steps). Presses on the reset lever returned the current to the first step, which produced the starting current. The electrical stimuli were delivered to the animal through an Airflyte commutator (Model CAY-675-6, Airflyte Electronics, Bayonne, NJ). The base of the commutator was connected to a length of spring-shielded hearing-aid wire (Plastic Products, Roanoke, VA), which was plugged into an electrode on the head of the animal.

Surgery and Histology

Rats were anesthetized with sodium pentobarbital (50 mg/kg, IP) and also given atropine sulfate (0.25 mg, SC) to reduce any respiratory discomfort. After placement in a stereotaxic device, the animals were implanted with bipolar platinum electrodes in the MFB-LH as described in our previous study [24]. The surgical procedure for implanting and removing the minipumps was as follows. Animals were lightly anesthetized by the inhalation of methoxyflurane (Metofane®, Pitman-Moore, Washington Crossing, NJ). An interscapular incision was made and the pump inserted subcutaneously with the delivery portal away from the incision. The wound was then closed with 2–3 wound clips. The pumps were removed under methoxyflurane anesthesia, and the incision was re-closed with wound clips. These procedures took only a few minutes. The osmotic minipumps (Model 2ML1, Alzet, Palo Alto, CA) were filled either with 60 mg/ml morphine in saline or with saline alone. Pumps were usually implanted on a Monday morning between 9:00–11:00 a.m. and removed the following Monday morning at the same time. The physical principles that determine pump performance have been previously described [25].

After the conclusion of the experiments, animals were overdosed with sodium pentobarbital and perfused via the heart with 10% formol-saline. Brains were mounted on a microtome stage, frozen and sectioned at 50 μm. Alternate sections were stained with cresyl violet and Weil's stain. The stained sections were viewed under a micro-projector to assure accurate location of the electrode tips.

Procedures

Starting a week after electrodes were implanted, rats were trained in the auto-titration procedure. At the beginning of each session, animals were rewarded with a suprathreshold stimulus on a continuous reinforcement schedule. After each 15th lever press the current was decreased by 5 μA. When the current was no longer reinforcing, animals were trained to turn around and press the reset lever; this reset the current to the initial suprathreshold level. Pressing the reset lever also produced a brief presentation from a Sonalert speaker; however, pressing the reset lever did not produce brain stimulation. Training continued until the threshold for each animal stabilized. To obtain baseline values for both response rates and thresholds, and to determine the acute effects of opioids on the auto-titration procedure, animals were first tested with small doses of morphine (0.3, 1.0, 3.0 mg/kg), naloxone (1.0 mg/kg), and saline. During this phase, which usually lasted two weeks, animals were tested in the auto-titration procedure for 20 min per day, four days per week. Animals were injected either with saline (Monday, Thursday) or drug (Tuesday, Friday) and tested 15 min later. After completing this phase, each animal was implanted with an osmotic minipump as described. Animals were then left undisturbed for four days at which time they were given a single dose of 3.0 mg/kg morphine, and tested in the ICSS threshold procedure to determine if tolerance to the rate-decreasing effects of morphine had developed. After this test, animals were again left undisturbed for three days, when the pumps were removed.

The two original groups of animals implanted with morphine- or saline-containing pumps were each further divided into two groups, resulting in four new groups. Group 1, the control group, consisted of 11 animals that received saline in their minipumps. During withdrawal, these animals received either saline (n=7) or 1.0 mg/kg naloxone (n=4). Since results for the two groups did not differ, they were combined into a single control group. Group 2, the spontaneous withdrawal group, consisted of 7 animals that received morphine in their minipumps and were injected with saline during withdrawal. Group 3, the precipitated withdrawal group, consisted of 9 animals that received morphine in their minipumps and were injected with naloxone during withdrawal. Starting four hours after removing the minipumps, animals were injected with the naloxone or saline, and 15 min later they were tested in the auto-titration procedure for 20 minutes. Over the next seven days the injection and testing procedures were repeated.

Immediately before removing the pumps and each morning thereafter, body weights were obtained. These were again obtained at the time of saline or naloxone administration and one hour after completing the auto-titration procedure. During this same 95 min period, the presence or absence of withdrawal signs was assessed using a checklist adapted from that of Collier *et al.* [5].

Drugs

Morphine sulfate (Merck and Co., Rahway, NJ), and naloxone hydrochloride (courtesy of Endo Laboratories, Garden City, NY) were used. They were administered subcutaneously (SC) in 0.9% saline. The SC injections consisted of 0.3, 1.0 and 3.0 mg/ml morphine and 1.0 mg/ml naloxone (both expressed as free base), and were administered in 1 ml/kg volumes. The SC infusions consisted of 10 μl/hr morphine (60 mg/ml, free base) or saline. This produced dose rates of 1.2 mg/kg/hr or 28.8 mg/kg/day in 500 g animals.

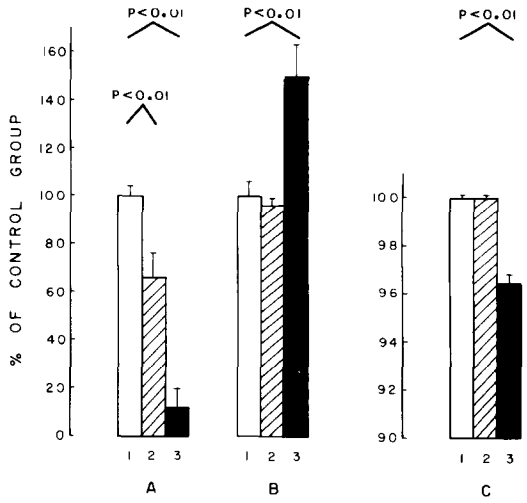

FIG. 1. A—Changes in the rate of lever-pressing for ICSS, B—changes in the reinforcement threshold for ICSS, and C—changes in body weight 95 min after saline/naloxone administration on the first day of withdrawal from morphine. In each of the three sections, 1 refers to the control group (n=11), 2 refers to the spontaneous withdrawal group (n=7), and 3 refers to the precipitated withdrawal group (n=9). Vertical bars above each group mean give standard error of mean (SEM). Data are expressed as a percentage of the control group's value. The ranges of values for all parameters were: A—rate of lever-pressing per 20 min: Group 1=1389–5338, 2=942–4439, 3=1523–5441; B—reinforcement threshold in μA: Group 1=61–159, 2=98–187, 3=62–160; C—body weight in g: Group 1=330–556, 2=396–451, 3=475–587.

Data Analysis

Data collected in the auto-titration sessions consisted of (1) the total number of lever presses on the stimulation lever per 20 min, (2) the current intensity at which the animal pressed the reset lever for each titration series, and (3) the total number of resets during the session. The average current intensity at which the animal reset the current to its starting value was defined as the reinforcement threshold. During morphine withdrawal, the data consisted of (1) numbers of lever presses per 20 min, (2) the reinforcement thresholds, (3) body weight changes within days and from day-to-day, and (4) the occurrence of withdrawal signs. The reinforcement threshold on each day of withdrawal was compared with the saline baseline threshold prior to the implantation of pumps and was expressed as a percentage of the baseline threshold value. Similarly, the number of responses on the stimulation lever was expressed as a percentage of the baseline response rate prior to chronic morphine infusion. On the first day of withdrawal, completely randomized analyses of variance were used to compare the control group with the spontaneous and naloxone-precipitated withdrawal groups on differences in response rates, reinforcement thresholds and within days weight changes [14]. Post hoc comparisons between groups were made with the Newman-Keul's procedure. Analyses of variance using a split-plot factorial design were used to evaluate the time-course of changes in response rates and reinforcement thresholds over the eight-day withdrawal phase. The

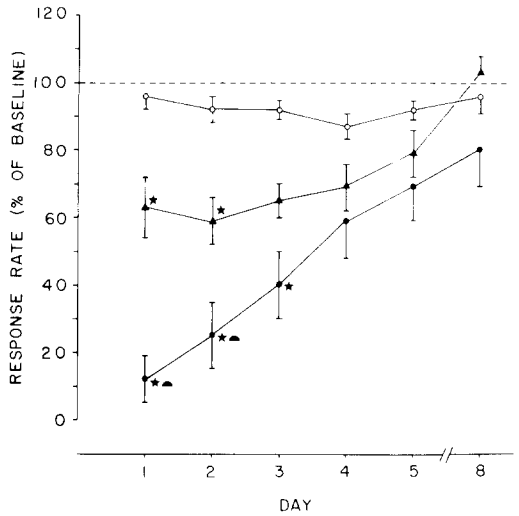

FIG. 2. The effects of withdrawal from morphine on the rate of lever-pressing for ICSS over an eight-day period. Symbols represent the control group (○), spontaneous withdrawal (▲) and precipitated withdrawal group (●). Horizontal interrupted lines in this and the subsequent figure give saline values during the Baseline period. Vertical bars give standard error of mean (SEM). ★—Significantly different from control group ($p<0.05$–0.01); ◓—significantly different from spontaneous withdrawal group ($p<0.05$–0.01).

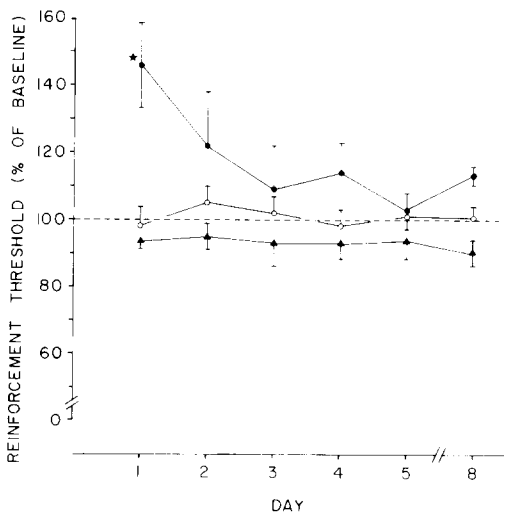

FIG. 3. The effects of withdrawal from morphine on the reinforcement threshold for ICSS over an eight-day period. Symbols represent the control group (○), spontaneous withdrawal group (▲) and precipitated withdrawal group (●). ★—Significantly different from control group ($p<0.05$–0.01).

TABLE 2

CHANGES IN BODY WEIGHT MEASURED DAILY AT 8:30 A.M. IMMEDIATELY PRIOR TO AND FOLLOWING REMOVAL OF PUMPS

		Day					
Group	N	1	2	3	4	5	8
(1) Control	11	101 ± 1	100 ± 1	100 ± 1	99 ± 1	98 ± 1	100 ± 1
(2) Spontaneous Withdrawal (Saline)	7	101 ± 1	93* ± 1	89* ± 1	87* ± 1	89* ± 1	95* ± 1
(3) Precipitated Withdrawal (Naloxone)	9	101 ± 1	93* ± 1	93*† ± 1	94*† ± 1	95† ± 0.5	98 ± 1

*$p<0.05$–0.01 Compared to control.
†$p<0.05$–0.01 Compared to spontaneous withdrawal.
Values are calculated as % of baseline weights.

Newman-Keuls' procedure was also used to evaluate differences between groups on each day of withdrawal. These procedures were also used to analyze body weight changes. Body weights measured in the morning were compared with the baseline body weights prior to pump implantation. Body weight changes measured within days consisted of calculating the difference between the beginning and end of the 95 min period. This difference was subtracted from the baseline weight and the result was computed as a percentage of the baseline weight to produce data independent of weight changes measured at 8:30 a.m. To evaluate differences in the occurrences of withdrawal signs, chi-square tests were used [4]. The number of animals in each group displaying specific withdrawal signs on each day of withdrawal was tallied and group differences compared.

RESULTS

General Observations—Tolerance and Withdrawal

Implantation and removal of the minipumps was a simple task. Animals recovered from surgery within 10 min and appeared completely normal 30 min later. The only observable difference between animals receiving saline and morphine infusions occurred approximately 4–5 hr after pump implantation. The spontaneous activity of the morphine-treated animals decreased and a modest Straub tail was observed [28]. This effect lasted several hours and subsided the day after pump implantation. Since our pumps were not primed, the nominal start-up time would have been about four hours which corresponded with the onset of the behavioral effects. In these experiments, morphine-treated animals

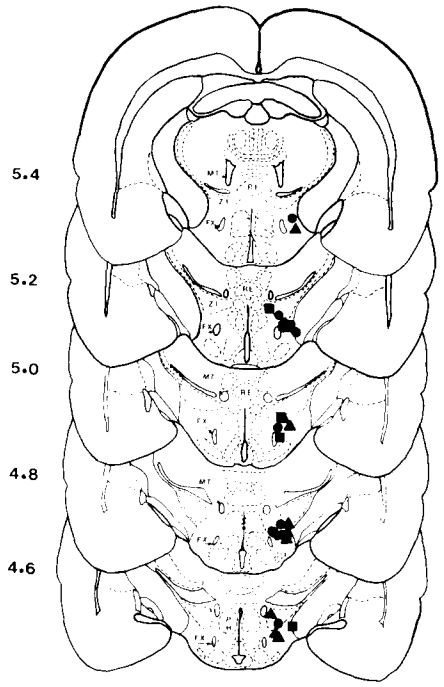

FIG. 4. Maps of the locations of the electrode placements for all animals used in these experiments. The symbols refer to the electrode placements for animals in the control group (●) (n=11), spontaneous withdrawal group (■) (n=7) and precipitated withdrawal group (▲) (n=9). These sections are adopted from Pellegrino *et al.* [20]. Numbers to the left of the sections indicate the anterior-posterior location of the section relative to interaural plane. Abbreviations: RE—nucleus reuniens thalami; MT—mamillothalamic tract; ZI—zona incerta; FX—fornix; PH—posterior nucleus of the hypothalamus.

did not lose weight, which was in marked contrast to our previous results when animals received twice daily injections [24]. Before the pumps were implanted, 3.0 mg/kg morphine reduced the rate of responding in the auto-titration task to 53±6% of the saline baseline score. Four days after the pumps were implanted, the same morphine dose reduced the rate to 58±7% in control animals and to 88±10% of baseline in animals implanted with morphine-containing pumps. This attenuated response (88 vs. 53%, 88 vs. 58%, $p<0.01$ in both cases) indicated that some degree of tolerance had developed (data not presented). After removing the pumps, they were cut crosswise and inspected as described in the Alzet literature. All pumps appeared to function as designed. Animals undergoing naloxone-precipitated withdrawal showed signs of withdrawal within 10 min of its administration. In addition to the signs listed in Table 1, seminal emissions and chromodacryorrhea occurred, particularly on the first two days. During this time, increased irritability to touch and handling was also observed and animals vocalized when placed in or removed from the operant chamber.

Withdrawal Day 1

The implantation and removal of the pump containing saline did not itself alter the rate of lever-pressing in the auto-titration procedure. The most marked effects were observed on the first day of withdrawal and are shown in Fig. 1. In animals undergoing spontaneous withdrawal by termination of the morphine infusion, a decrease to 66% of the rate of lever pressing by the control group was observed ($p<0.01$). Animals undergoing precipitated withdrawal with naloxone showed a greater decrease to 12% of the control group ($p<0.01$) and the overall analysis was highly significant, $F(2,24)=45.4$, $p<0.001$ (Fig. 1A). A different pattern of effects was seen on reinforcement thresholds, $F(2,24)=11.4$, $p<0.001$. In the spontaneous withdrawal group there were no changes in the reinforcement threshold, while in the precipitated withdrawal group the threshold was significantly elevated ($p<0.01$) (Fig. 1B).

The changes in body weight following saline and naloxone administration on the first day of withdrawal are illustrated in Fig. 1C. Again, there was a significant decrease ($p<0.01$) only in the precipitated withdrawal group, $F(2,24)=77.5$, $p<0.001$. This could be attributed to the high incidence of diarrhea shown by animals in this group, $\chi^2(2)=21.08$, $p<0.001$ (Table 1). In addition, there were other differences in the occurrence of withdrawal signs on Day 1. Unlike control animals and animals undergoing spontaneous withdrawal, a significantly larger proportion of animals in the precipitated withdrawal group showed the following signs: irritability to touch or handling, $\chi^2(2)=22.7$, $p<0.001$; body shakes, $\chi^2(2)=15.5$, $p<0.001$; and salivation, $\chi^2(2)=22.7$, $p<0.001$.

Time-Course of Withdrawal Effects

Figure 2 shows the time course of changes in the rate of responding starting on the first day of withdrawal (Monday) until the following week (Monday) when withdrawal had appreciably subsided. The data are shown as percent of baseline values. All three F-ratios in the factorial analysis were significant: withdrawal conditions, $F(2,24)=23.7$, $p<0.001$; days, $F(5,120)=13.9$, $p<0.001$; conditions by days, $F(10,120)=6.6$, $p<0.001$. The rates for animals in the spontaneous withdrawal group were significantly reduced the first and second day with a gradual return starting on the third day. In the precipitated withdrawal group the reductions were more severe and lasted longer. The pattern of changes in reinforcement threshold was different (Fig. 3). Only the F-ratio for withdrawal conditions was significant, $F(2,24)=7.7$, $p<0.005$, and this was due to the significant increase in thresholds for the precipitated group on the first day.

Changes in 8:30 a.m. body weights are shown in Table 2. On the first day, just before the pumps were removed, none of the animals had lost weight. By the following morning both morphine-treated groups had lost weight and highly significant analyses of variance resulted: conditions, $F(2,24)=24.3$, $p<0.001$; days, $F(5,120)=112.6$, $p<0.001$; conditions by days, $F(10,120)=29.3$, $p<0.001$. Animals in the spontaneous withdrawal group weighed significantly less than control animals throughout the eight days. Animals in the precipitated group weighed less than control animals through the fourth day, but then began regaining body weight faster than animals in the spontaneous withdrawal group. Changes in body weight during the 95 min period between the time of injection and one hour after the ICSS test session present a different profile of effects. All three F-ratios were significant: conditions, $F(2,24)=42.4$, $p<0.001$; days, $F(5,120)=16.8$, $p<0.001$; conditions by days, $F(10,120)=11.0$, $p<0.001$. Animals in the control and spontaneous withdrawal groups lost less than 1% of their baseline body weight. In contrast, animals in the precipitated withdrawal group lost significantly more weight than groups 1 and 2

on the first three days of withdrawal (data not shown). More animals in the precipitated group showed signs of withdrawal. In addition to the effects noted above for Day 1, on Day 2 these animals showed a higher incidence of diarrhea, $\chi^2(2)=19.1$, $p<0.001$; and irritability to touch or handling, $\chi^2(2)=12.1$, $p<0.001$. On Day 3, $\chi^2(2)=27.0$, $p<0.001$; and Day 4, $\chi^2(2)=9.4$, $p<0.01$, animals in the precipitated withdrawal group also had a higher occurrence of diarrhea. No withdrawal signs were observed after Day 4.

Histology

Figure 4 shows the distribution of the sites of electrode tips for the control, spontaneous withdrawal and precipitated withdrawal groups. The electrode tips terminated in or near the lateral hypothalamus and adjacent zona incerta, fornix and internal capsule. The tip locations were evenly distributed over the AP range of 4.6–5.4.

DISCUSSION

These experiments demonstrated that morphine withdrawal can produce significant changes in the reinforcement threshold for brain-stimulation in the medial forebrain bundle. The extent of the changes in threshold and in operant behavior depended upon whether the animals experienced spontaneous or naloxone-precipitated withdrawal. Both conditions produced reductions in the rate of lever-pressing, but only precipitated withdrawal elevated the reward threshold.

When morphine is administered to opiate-naive animals, the effects on the rate of lever-pressing for ICSS depend upon the dose and time since injection. Low doses may produce a modest increase. Moderate-to-high doses produce an initial decrease followed several hours later by an increase [16,23]. The effects of acute morphine administration on the reinforcement threshold are quite consistent; most investigators report that the drug lowers the threshold ([15,18] and present data). In contrast to examining acute effects, this and our previous report [24] have systematically evaluated the consequences of morphine withdrawal on behavior reinforced with ICSS. During withdrawal the effects on rewarded behavior were generally the opposite to those produced in opiate naive animals. In both sets of experiments removal of morphine resulted in a decrease in the rate of responding which was most severe on the first day and gradually subsided over the course of a week. When, in addition, naloxone was administered, the decrease in response rate was magnified. The reductions in the rate of lever-pressing appeared to be somewhat greater in this study than in our previous report for both withdrawal conditions (compare Fig. 1 in [24] with Fig. 2 in this report). Previously, animals were given twice daily SC injections (30 mg/kg/day) for four days. While the total daily administration of morphine was approximately equal to that used in the present experiment, there were two important procedural differences. First, we used an infusion technique rather than a bolus injection, and in these experiments the rats were exposed to morphine for seven rather than four days. However, the tasks (single lever vs. autotitration) were quite different and this alone might have accounted for the differences in response rates.

Changes in body weight have long been used as a reliable index of morphine withdrawal [1,8] and were also used in these studies. When the animals were weighed in the morning a significant reduction in body weight was observed starting on Day 2, and both the percentage of weight loss and the time course were similar to our previous study [24]. When body weights were measured within days, a different pattern of effects occurred. For control animals injected with either saline or naloxone and for animals in the spontaneous withdrawal group administered saline, less than 1.0% of body weight loss occurred. This modest loss ($\leq$5 g) is not unusual in animals lever pressing for ICSS. In contrast, animals in the naloxone-precipitated withdrawal group lost significantly more weight than all the other animals during the first three days of withdrawal; the effect was most pronounced on the first day. Our results complement those of Gellert and Sparber [6]. In their paradigm rats were trained on a fixed-ratio 20 schedule of food presentation, and following the SC implantation of a 75 mg morphine pellet, naloxone produced both weight loss and reductions in the rate of responding for food.

In the naloxone-precipitated withdrawal group we also found a number of physiological (diarrhea, salivation) and behavioral (irritability to touch or handling, body shakes) signs that occurred during the first four days of withdrawal. Particularly noteworthy was the correspondence between diarrhea and loss of body weight when measured 95 min after naloxone, an effect noted with both morphine pellets and morphine drinking solutions [3,10]. Furthermore, the degree of diarrhea and weight loss previously demonstrated was a function both of the dose of naloxone and the interval between morphine termination and naloxone administration.

These results demonstrated that morphine infused subcutaneously from minipumps will produce an abstinence syndrome qualitatively similar to other techniques including multiple injections, pellet implants and morphine-diluted drinking water. We are aware of only one brief report [17] in which low doses of morphine (approximately $^1/_{10}$ that used in these experiments) infused subcutaneously from minipumps produced an abstinence syndrome in rats when tested at seven days. Several investigators have rendered animals dependent on morphine using minipumps to infuse the drug into the brain's ventricular space [11, 26, 27] and these studies have described withdrawal patterns in detail following direct CNS drug application. Our experiments provide systematic descriptions of the physiological and behavioral changes occurring during withdrawal when a constant dose of morphine is infused peripherally. We have observed that: (1) there are reductions in operant behavior for ICSS, and these reductions are greater during naloxone-precipitated than during spontaneous withdrawal, (2) during precipitated withdrawal there are increases in the reward threshold, and this effect is the opposite of that produced by morphine in opiate-naive animals, and (3) in the precipitated withdrawal group there are physiological changes including diarrhea and weight loss that correspond with the changes in operant behavior. There has been much emphasis on the physiological changes occurring during opiate withdrawal and these results show good concordance between the animal and human studies [13,21]. Our results extend these findings to more complex behavior and suggest that the changes in operant behavior and, in particular, the changes in reinforcement thresholds may be analogous to the well-documented conditions of anxiety, anhedonia and depression observed in addicts during opiate withdrawal.

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