The role of self-administration in morphine withdrawal in rats

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Rats assigned to a self-administration-of-morphine group (SA-M) could press a lever in an operant chamber to deliver an intravenous infusion of morphine to themselves and to a yoked morphine (Y-M) rat, and an infusion of Ringer's solution to another yoked rat. Although rats assigned to SA-M and Y-M groups received the same drug doses at the same time, withdrawal symptoms were more pronounced in SA-M rats. Possible mechanisms for the differences in drug withdrawal between animals that self-administer morphine and animals that passively receive the drug are discussed.

There is increasing evidence that the effects of a variety of drugs are different if they are self-administered rather than passively received. For example, Moolten and Kornetsky (1990) evaluated the ability of ethanol to reduce the threshold of rewarding electrical brain stimulation (a putative measure of drug-induced euphoria). They found that ethanol reduced the stimulation threshold in rats that self-administered ethanol (by drinking a sucrose ethanol solution), but not in rats that had ethanol intragastrically infused at the same rate as that at which self-administrators consumed the drug.¹ Ator and Griffiths (1993) evaluated the effect of a series of intravenous midazolam infusions on the discriminative stimulus effects of the tranquilizer. They found that when 2 baboons self-administered midazolam, their sensitivity to the stimulus effects of the drug increased. In contrast, when they received the drug in a response-independent manner (in a pattern that mimicked their self-administration protocol), their sensitivity to the stimulus effects of midazolam decreased.

Reports that self-administered drugs are less toxic than passively received drugs provide especially dramatic evidence for the importance of the self-administration contingency. Johanson and Schuster (1981) discuss findings suggesting that experimenter-programmed administration of phencyclidine in monkeys frequently is lethal "at dose levels at or below those self-administered, which animals survived" (p. 280). They suggested that the role of self-administration in drug lethality should be assessed in species more readily available than primates, such as rats. Just that has been done by S. I. Dworkin and colleagues (S. I.

Dworkin, Mirkis, & Smith, 1995; S. M. Dworkin, Volkmer, & S. I. Dworkin, 1988). They evaluated the effects of cocaine in rats, using a yoked-control design. Each time a rat assigned to a self-administration group pressed a lever to obtain intravenous cocaine, the same amount of drug was administered to that subject and to another, yoked rat. Mortality was significantly lower in rats that self-administered cocaine than it was in their yoked partners. The results of additional cocaine research indicate that the neurochemical effects of the drug (Kiyatkin & Stein, 1995; Wise et al., 1995) and the neurochemical alterations seen during cocaine withdrawal (S. I. Dworkin, Co, & Smith, 1995) are different in rats that self-administer cocaine than in rats that passively receive cocaine.

The yoked-control design has also been used in several experiments concerning the effects of opiates in rats. Smith and colleagues have reported that self-administering and yoked rats differ in neurotransmitter turnover rates (Smith, Co, Freeman, & Lane, 1982; Smith, Co, Freeman, Sands, & Lane, 1980; Smith, Co, & Lane, 1984a; Smith & Lane, 1983) and receptor densities (Smith, Co, & Lane, 1984b). Moreover, following presentation of a tone that had been paired with infusion of heroin, rats that had self-administered the drug displayed different patterns of localized cerebral metabolic activity than did rats yoked to these self-administrators (Trusk & Stein, 1988).

Mello and Mendelson (1970) presented perhaps the first demonstration that self-administration modulates the effects of a drug. The results of their experiment suggested that self-administration augments drug withdrawal symptoms. Alcoholic men were allowed to ingest alcohol in each of two conditions: when they wished (spontaneous condition) or only during experimenter-determined intervals (programmed condition). Withdrawal distress following removal of the drug was greater in the same individuals following the spontaneous than following the programmed condition. The present experiment was designed to evaluate the effects of self-administration on opiate withdrawal symptoms. Opiate withdrawal behaviors were evaluated in rats that self-administered morphine, as well as in rats yoked to these self-administrators.

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METHOD

Subjects and Surgical Preparation

The subjects were 18 experimentally naive male Long-Evans hooded rats, weighing between 385 and 620 g at the time of surgery. The rats were individually housed in clear, plastic cages, with food and water available ad lib. The animal colony was maintained on a 16:8-h light:dark cycle. All experimental sessions were run during the light phase.

Intravenous catheters were implanted in the right jugular vein under sodium pentobarbital anesthesia, using a modified version of the technique of R. J. Brown and Breckenridge (1975). The catheters, based on the Plastic Products C-313 cannula equipment system (Plastic Products, Roanoke, VA), were made of silastic tubing (.03-cm inner diameter $\times$.06-cm outer diameter). The tip of the catheter was located approximately 1 cm from the heart. The cannula was anchored to the jugular, and was passed subcutaneously to the top of the skull where a cannula guide was anchored in place with dental cement. The catheter was flushed with a solution of heparin and antibiotic (65 μ g of sodium heparin and 1.25 mg of ampicillin) and sealed with a screw-on cannula cap. The catheters were flushed with heparin/antibiotic solution on the 3rd, 5th, and 7th days following surgery. The experimental procedure started between 8 and 14 days following surgery. On the day prior to initiation of experimental manipulations, all animals were infused with heparin/antibiotic solution to ensure both patency and integrity of the catheter.

Drugs and Apparatus

Drugs. A solution of 10-mg/ml morphine sulfate (Allan & Hanbury, Toronto) dissolved in lactated Ringer's solution was used. The solution was infused at a rate of .023 ml/sec for a period of 3 sec. Each infusion, therefore, consisted of a constant dose of .69 mg of morphine sulfate delivered in .069 ml of vehicle. Vehicle-alone infusions followed these rate and time parameters.

Operant chambers. Three operant chambers (30.4 $\times$ 20.5 $\times$ 19.0 cm, Lehigh Valley Electronics), fitted with water bottles, were used. All chambers were equipped with one response lever. A small stimulus light was mounted above the lever. The chambers were located in sound-attenuating vented cubicles. Each sound-attenuating cubicle was fitted with a hydraulically sealed swivel (modified version of that described by Z. W. Brown, Amit, & Weeks, 1976) that allowed the rats free movement while they were attached to the infusion apparatus. The subjects were connected to the swivels by a spring-protected cannula connector. Polyethylene tubing (PE-90) connected the swivel to a 20-cc syringe (with an in-line 0.22-micrometer micropore filter unit, Millex-GS) held in a Sage Instruments Model 341A syringe pump. The houselight of each box was programmed to turn off while the lever in that box was depressed. In addition, leverpresses in one of the three boxes (the one dedicated to the self-administering rats) led to infusions in all boxes. Illumination of the stimulus lights above each lever occurred during the period coincident with each infusion.

Procedure

The rats were divided into six triplets matched individually on the basis of body weight. Within each triplet, a rat was randomly assigned to one of three groups: self-administration of morphine (SA-M), yoked morphine (Y-M), and yoked Ringer's solution (Y-R). Each triplet participated in the experiment for three, consecutive, week-long cycles. The 1st day of each cycle consisted of one 3-h infusion session in the operant chamber. Leverpresses by the SA-M rat delivered morphine to it (on a continuous reinforcement schedule) and to the Y-M rat (and Ringer's solution to the Y-R rat). No additional drug was delivered as a consequence of a leverpress by an SA-M rat during a 3-sec infusion period. Leverpresses by Y-M and Y-R rats had no consequences other than the offset of the houselight in their respective chambers for the duration of the leverpress.

The 2nd through 6th days of each cycle consisted of two 3-h infusion sessions in the operant chamber, separated by 3-h intervals. Thus, subjects received a total of 11 infusion sessions during the first 6 days of each cycle.

The 7th day of each cycle consisted of one 2-h withdrawal test which was identical to the drug sessions, with the exception that the doors to the sound-attenuating chambers were left open (to facilitate observation) and the infusion pumps were turned off.

Assessment of Withdrawal

During each withdrawal test, the rats were placed into the operant chambers and withdrawal scoring commenced immediately, with each successive 5-min period devoted to the observation of another one of the 3 rats. Each rat received eight observation periods during each test. All withdrawal tests were scored by an experimenter who was aware of subject group assignment. To evaluate possible bias effects, this primary observer's assessments were compared with those of a second observer on 4 of the 18 withdrawal tests. This second observer was trained in scoring withdrawal signs, but ignorant of the design and intent of the study. Seven categories of withdrawal behaviors were derived from the withdrawal evaluation procedures previously employed by a number of investigators:

1. Body shakes (e.g., Badawy, Evans, & Evans, 1982; Collier, Francis, Henderson, & Schneider, 1974; Leung, Ogle, & Dai, 1986): a movement similar to that displayed by a dog shaking water off its body. The movement tends to "crawl up" the back and usually includes the head and shoulders.
2. Head shakes (e.g., Badawy et al., 1982; Collier et al., 1974; Leung et al., 1986): similar to a body shake, but restricted to the head and shoulders area.
3. Teeth chattering (e.g., Collier et al., 1974; Laschka, Herz, & Blasig, 1976; Leung et al., 1986): a rat scored one teeth chatter if rapid jaw movements coincided with an audible chattering sound.
4. Paw tremors (e.g., Badawy et al., 1982; Collier et al., 1974; Leung et al., 1986): a rat scored one paw tremor each time one or both of the forepaws vibrated quickly with no grooming-related function apparent.
5. Ear wiping (e.g., Gianutsos, Drawbaugh, Hynes, & Lal, 1975; Glick, Rossman, Rao, Maisonneuve, & Carlson, 1992): a rat scored one ear wipe each time it was grooming and pulled both paws simultaneously over the ears from the back to front.
6. Mouthing (e.g., Badawy et al., 1982; Collier et al., 1974; Laschka et al., 1976): a rat scored one mouthing behavior when a burst of nondirected jaw movements (with or without concomitant tongue protrusions) occurred.
7. Rearing (e.g., Azorlosa, Hartley, & Deffner-Rappold, 1994; Falls & Kelsey, 1989): a rat scored one rear for each instance that it stood up on its hind legs and extended its upper body upward. Grooming periods when the forepaws were off the floor were not counted as rears.

In addition to tabulation of the individual withdrawal behaviors for each rat on each test session, a withdrawal score was computed. This score was the total of all withdrawal behaviors.

RESULTS

Two rats assigned to group Y-R died in the final (third) weekly cycle of the experiment. No data from these subjects are included in any analyses of data from this week (excluding all the data from these subjects would not appreciably affect the patterns of results or the conclusion).

Morphine Delivered

Figure 1 summarizes the mean amount of morphine delivered per session for each day of the experiment. As can be seen in Figure 1, the mean amount of morphine de-

livered (as a result of responding by SA-M subjects) increased over the course of training. A repeated measures analysis of variance of the data summarized in Figure 1 indicated significant effects of week and of session [$F(2,10) = 9.19$ and $F(10,50) = 2.75$, respectively, $ps < .01$].

Withdrawal Symptoms

Reliability of scoring. A Spearman rank-order correlation of the data from the four withdrawal tests sessions during which two observers independently scored withdrawal signs displayed by each rat in a triplet indicated that the measure was reliable. The rank-order correlation of withdrawal scores ($n = 12$) between the two observers was $+ .98$.

Group differences. For every rat, the mean number of each of the withdrawal behaviors displayed on each of the test sessions was computed. Although the amount of morphine delivered increased over sessions (see Figure 1), neither the withdrawal scores, nor any of the individual withdrawal behaviors, increased over the course of the three test sessions. Thus, withdrawal behaviors were asymptotically displayed on the first test session. The mean frequency of occurrence of each withdrawal behavior (across all test sessions) displayed by rats in the three groups is shown in Figure 2. The pattern of results apparent in Figure 2 was seen in each of the three test sessions. That is, on each session, rats assigned to Group SA-M displayed more withdrawal symptoms than did rats assigned to Group Y-M.²

The pattern of results apparent in Figure 2 was observed in each of the six triplets. Figure 3 displays the mean withdrawal scores (across all test sessions) for every triplet (in the order in which they were run). Wilcoxon signed-ranks tests indicated that all pairwise differences (SA-M vs. Y-M, Y-M vs. Y-R, and SA-M vs. Y-R) were statistically significant [all $T_s(6) = 0$, $ps < .05$]. Withdrawal scores did not change significantly across the three with-

drawal test sessions (each withdrawal test session occurring at the end of 11 infusion sessions over 6 days). That is, with the procedures used in this experiment, the display of withdrawal behaviors was asymptotic by the end of the 1st week.

DISCUSSION

The effects of morphine are different in rats that self-administer the drug (Group SA-M), compared with rats that passively receive the same doses of drug, equally often, and at the same times (Group Y-M). Previous opiate research has indicated that the self-administration contingency affects neurotransmitter turnover rates (Smith et al., 1984a; Smith et al., 1982; Smith et al., 1980; Smith & Lane, 1983), receptor densities (Smith et al., 1984b), and localized cerebral metabolic activity (Trusk & Stein, 1988). The present results suggest that withdrawal symptoms are more pronounced in SA-M than in Y-M rats.

Interpretation of Different Effects in Self-Administering and Yoked Subjects

Although it seems clear that self-administered drugs have effects different from those of passively received drugs, the basis for the difference is uncertain. There are several ways in which the effect of a series of drug administrations may be different in self-administering subjects than in their yoked partners.

Self-administered drugs as predictable drugs. Several investigators have noted that, in research concerning the effects of event controllability, there typically is confounding between controllability and predictability (e.g., Averill, 1973; Overmier, Patterson, & Wielkiewicz, 1980). One obvious explanation for differences between self-administered and passively received drugs emphasizes the fact that the former is predictable and the latter is not. That is, there are internal cues available to self-administrators

Figure 1. Mean amount of morphine delivered on each infusion session of the experiment.

Figure 2. Mean frequency of occurrence of each withdrawal behavior by rats assigned to Groups SA-M, Y-M, and Y-R.

that signal imminent pharmacological stimulation (e.g., cognitive-volitional or proprioceptive signals for drug administration), but there are no such cues for yoked animals. There is an extensive literature concerning modulation of passive drug effects by predrug signals, and this literature may be relevant to understanding modulation of drug effects by self-administration. For example, tolerance occurs more rapidly when each drug administration is preceded by a reliable signal, rather than a changing signal (Epstein, Caggiula, Perkins, McKenzie, & Smith, 1991) or no signal (Siegel, Hinson, & Krank, 1978). Moreover, following repeated drug administrations, the display of morphine tolerance typically is greater if the drug is presented in the presence of the usual drug administration cues rather than in the presence of alternative cues (see reviews by Siegel, 1989; Siegel & MacRae, 1984). Similarly, the display of withdrawal symptoms (and postabstinence relapse to self-administration) often is especially pronounced in the presence of environmental stimuli that have been paired with morphine in the past (e.g., Azorlosa et al., 1994; Hinson, Poulos, Thomas, & Cappell, 1986; Siegel, 1988; Thompson & Ostlund, 1965).

Although there are various interpretations of the contribution of predrug cues to tolerance and withdrawal effects (see reviews by B. R. Dworkin, 1993; Poulos & Cappell, 1991; Siegel, 1989, 1990; Stewart & Eikelboom, 1987), one theory emphasizes the contribution of drug-compensatory conditional responses (CRs). That is, as suggested by Pavlov (1927), the administration of a drug constitutes a conditioning trial. Conditional stimuli (CSs) are cues present at the time of drug administration, and the unconditional stimulus (UCS) is the drug effect. The pharmacological UCS elicits homeostatic responses that attenuate the effect of the drug. Following repeated drug administrations, anticipatory homeostatic responses (drug-compensatory CRs) are elicited by drug-predictive CSs.

These CRs attenuate the effect of the drug administered in the context of the usual predrug cues. Thus, tolerance is especially pronounced when the drug is signaled (i.e., administered in the presence of the usual predrug cues), but not when the drug is unsignaled (i.e., administered in the presence of cues that have not been paired with the drug) (see MacRae, Scoles, & Siegel, 1987; Siegel, 1991). When the usual predrug cues are not followed by the usual pharmacological consequences, these drug-compensatory CRs are clearly evident (they are unmodulated by any drug effect). Many instances of "withdrawal symptoms" are (on the basis of this conditioning interpretation) actually drug-compensatory CRs elicited by drug-signaling stimuli (Siegel, 1988, 1991).

Self-administration may provide internal cues for a drug that function like external signals. That is, interoceptive cues accompanying self-administration, in common with external signals, may elicit anticipatory homeostatic responses. Thus, according to this analysis, drugs are functionally signaled for SA-M rats, but not for Y-M rats. Since both the SA-M and Y-M rats had the same contextual cues paired with the drug (the operant chamber), the interoceptive cues accompanying self-administration would (according to this analysis) overshadow these context cues. Overshadowing has been demonstrated in pharmacological conditioning (e.g., Dafters & Bach, 1985; Walter & Riccio, 1983).

Self-administration as optimized drug delivery. Several investigators (e.g., Black, 1967; Church, 1964; Moore & Gormezano, 1961) have noted a general feature of the yoked control procedure: differences between the experimental subject (which must respond to receive the reinforcer) and its yoked partner may reflect individual differences in sensitivity to the reinforcer. There very likely are individual differences in the pharmacokinetics and pharmacodynamics of morphine. When an SA-M rat re-

Figure 3. Mean withdrawal scores for each triplet of rats (in the order in which they were run in the experiment).

sponds for morphine, it may be doing so when the rewarding effect is particularly propitious. For example, it may be undergoing some opiate withdrawal, or otherwise be in a state in which the drug is reinforcing. Thus, an animal allowed to self-administer morphine will be able to time the delivery of each dose in such a way as to optimize the drug's efficacy. An animal yoked to such a self-administering partner enjoys no such privilege. Its doses occur in a pattern independent not only of its behavior, but also of its current physiological state.

Although differential optimization provides a mechanism whereby the drug may have different biological effects in SA-M and Y-M animals (Smith et al., 1984a, 1984b; Smith et al., 1982; Smith et al., 1980; Smith & Lane, 1983), the specific mechanisms whereby these different effects are manifest as differences in withdrawal severity are unclear.

Implications for Addiction Research

Regardless of the mechanism, the differences seen between SA-M and Y-M rats have implications for addiction research. Rats that self-administered morphine displayed clear evidence of drug withdrawal following the first, 6-day cycle of drug administration. Over the course of these 6 days rats received, on the average, a total of less than 75 mg of morphine. Typically, when morphine withdrawal symptoms are studied in rats, a passive administration procedure is used, and a much more prodigious history of drug administration is thought to be necessary (e.g., Aceto, 1990; Gianutsos et al., 1975). When withdrawal symptoms have been seen following small doses of morphine, the symptoms have been precipitated with an opiate antagonist (e.g., Krystal & Redmond, 1983; Ritzmann, 1981). It is possible that the amount of

morphine necessary to induce dependence (as evidenced by the spontaneous occurrence of withdrawal symptoms following termination of drug administration) has been overestimated because of the typical, passive administration procedures.

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NOTES

1. Although passively received ethanol may not be as effective as self-administered ethanol in modulating intracranial reward processes, the effect is relative rather than absolute. A number of investigators have demonstrated that there are circumstances in which passively received ethanol (intraperitoneally injected) reduces the threshold of rewarding electrical brain stimulation (see Lewis & June, 1994).

2. As can be seen in Figure 2, for some categories some "withdrawal" behaviors were noted in Group Y-R rats. That is, some behaviors that were indistinguishable from opiate withdrawal behaviors occurred in drug-naïve rats. Although the occurrence of these withdrawal-mimicking behaviors indicates some "noise" in the assessment of withdrawal, the statistical analyses indicate that the frequencies of these behaviors in Y-R rats was relatively small (compared with the frequencies in SA-M and Y-M rats).