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Conditioned Sucrose Aversions Produced by Naloxone-Precipitated Withdrawal From Acutely Administered Morphine

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MCDONALD, R. V., L. A. PARKER AND S. SIEGEL. *Conditioned sucrose aversions induced by naloxone-precipitated withdrawal from acutely administered morphine.* PHARMACOL BIOCHEM BEHAV **58**(4) 1003–1008, 1997.—The aversive properties of acute naloxone-precipitated morphine withdrawal were examined in the taste reactivity paradigm. Acute naloxone-precipitated withdrawal paired with sucrose solution established conditioned active rejection of the sucrose solution. Active rejection of sucrose was observed when naloxone was administered both 1 h and 22 h after morphine. When the stimulus properties of morphine were present during the conditioning trial, the conditioned sucrose aversion was only expressed when the rats were tested in the same drug state in which they had learned the aversion. However, when the stimulus properties of morphine were not present during conditioning, the aversion was expressed in the absence of the morphine state. The results suggest that palatability shifts can be conditioned to sucrose paired with acute morphine withdrawal.

Taste aversion Taste reactivity Morphine withdrawal Morphine Addiction Learning Rat

RATS avoid consuming a flavored solution that has previously been paired with an emetic agent, such as lithium chloride [e.g., (4)]. Conditioned taste avoidance may be produced not only by drug-induced sickness, but also by withdrawal from chronic morphine administration (3,11,15,16,20–22). Morphine withdrawal typically is produced by either terminating chronic morphine exposure or by administering an opiate antagonist to morphine pretreated rats (8).

Withdrawal symptoms may be precipitated by an opioid antagonist after only a few widely spaced administrations of an opioid (10,12,23); this phenomenon has been called acute physical dependence (12). Results of animal and human studies indicate that the symptoms of acute physical dependence are qualitatively similar to those seen following long-term opioid exposure (7,9,12). We report results of experiments investigating the aversive properties of withdrawal from acute morphine exposure using the taste aversion learning paradigm.

Although withdrawal from chronic exposure to morphine produces taste avoidance, it is not clear that this avoidance is motivated by a shift in the palatability of the drug-paired taste, i.e., taste aversion. The palatability of a taste can be directly assessed by the taste reactivity (TR) test (6). When rats are exposed to a highly palatable taste, such as sucrose solution, they display a characteristic set of ingestive reactions that includes tongue protrusions, mouth movements, and paw licking. On the other hand, during exposure to a highly unpalatable taste (such as quinine), rats display a characteristic set of rejection reactions that include gaping, chin rubbing, and paw treading. These rejection reactions are also elicited by a highly palatable taste (such as sucrose solution) that has previously been paired with an emetic drug (such as lithium chloride), suggesting that the taste becomes conditionally unpalatable or conditionally aversive.

Not all drugs that produce conditioned taste avoidance (as measured by a consumption test) produce a conditioned taste aversion (as measured by a TR test). Parker and colleagues [e.g., (17,18)] have demonstrated that although rats fail to consume a flavor paired with a rewarding drug (such as amphetamine, morphine, or cocaine), they do not actively reject it in the TR test. Additionally, rats do not reject a flavor

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paired with the opiate antagonist naltrexone, even following four conditioning trials with a high dose (10 mg/kg) capable of producing a strong place aversion (19). The ability of naloxone-precipitated withdrawal from acute morphine administration to motivate a conditioned taste aversion in the TR paradigm was examined in the following experiments.

EXPERIMENT 1

The first experiment was designed to evaluate the effect of naloxone precipitated withdrawal on sucrose palatability, as measured by the TR test. The design of this experiment was similar to that of previous experiments that employed taste-avoidance assessments of withdrawal [e.g. (15,16,20–22)]. During TR conditioning trials, one group of rats was treated with morphine before sucrose exposure and administered naloxone after sucrose exposure. Thus, rats in this group had sucrose paired with morphine withdrawal, but also experienced the sucrose-withdrawal pairing while narcotized.

EXPERIMENT 1A

Rats were injected with either 20 mg/kg of morphine or with physiological saline one hour prior to receiving an intraoral infusion of sucrose solution. Immediately following the sucrose infusion, they were injected either with 1 mg/kg of naloxone or with saline. Group designations indicate both the drug administered before the sucrose infusion (the "pre-sucrose drug"), morphine (M) or saline (S), and the drug administered following the sucrose infusion (the "post-sucrose drug"), naloxone (N) or saline (S). Thus, rats were assigned to one of four experimental groups as follows: Morphine-Naloxone (M-N), Morphine-Saline (M-S), Saline-Naloxone (S-N) or Saline-Saline (S-S).

METHOD

Subjects

Forty-two male Sprague–Dawley rats (Charles River Labs, St. Constant, Quebec) weighing 385–475 g on the first conditioning trial served as subjects. They were housed individually in wire mesh cages and maintained on ad lib food and water except as indicated.

Drugs

Naloxone HCl (Dupont) was mixed with saline at a volume of 1 mg/ml and administered intraperitoneally (IP). Morphine sulphate (British Drug House) was mixed with saline at a volume of 10 mg/ml and administered subcutaneously (SC). Physiological saline control injections were the same volume as the morphine or naloxone injections.

Procedure

One week after arriving in the laboratory, the rats were surgically implanted with the intraoral cannulae [for description of surgical procedures, see (17,18)]. They were allowed to recover for 1 week before they were adapted to the taste reactivity procedure. On each of three adaptation trials (separated by 24 h), the rats received an intraoral infusion of water at the rate of 1 ml/min for a 2-min period in the TR test chamber ($25.2 \times 26 \times 20$ cm).

TR conditioning trials 1–3. On the day following the final adaptation trial, rats received the first of 3 TR conditioning trials. Trials 2 and 3 occurred at 72-h intervals. Rats were randomly assigned to groups M-N ($n = 12$), M-S ($n = 11$), S-N ($n = 11$), or S-S ($n = 8$).

On each of the three conditioning trials, rats were injected with 20 mg/kg morphine (groups M-N and M-S) or saline (groups S-N and S-S) 60 min prior to being placed in the TR chamber. In the chamber, rats were intraorally infused with .5 M (17%) sucrose at the rate of 1 ml/min for 2 min. Their orofacial reactions during the 2 min infusion were videotaped. Immediately following the infusion, the rats were injected with either 1 mg/kg naloxone (groups M-N and S-N) or saline (groups M-S and S-S) and they were returned to their home cages.

Drug-free TR and consumption test trial. Three days after the third conditioning trial, all rats received a 2 min TR test trial in which they received neither the presucrose injection nor the postsucrose injection. Immediately following the TR test trial, rats were presented with sucrose and water in graduated drinking tubes in their home cages for a 120-min period. The amounts of each fluid consumed was measured and converted to sucrose preference ratios (volume of sucrose consumed/volume of sucrose + water consumed).

TR Analyses

The videotaped TR data were scored, by a rater blind to experimental groups, using a computer event recorder program ("The Observer," Noldus, Inc, NL). The frequency of each of the following behaviors was recorded: gaping (rapid, large-amplitude opening of the mandible with concomitant retraction of the corners of the mouth), chin rubbing (mouth or chin in direct contact with a floor or wall and projecting the body forward or upward), and paw pushing (sequential extension of one forelimb forward against the floor while the other forelimb is being retracted). The frequency of each of the three reactions was summated to provide a single rejection score.

RESULTS AND DISCUSSION

TR Conditioning Trials 1–3

Figure 1 presents the mean frequency of rejection reactions displayed by the various groups on conditioning trials 1–3 of Experiment 1A. Rats that had sucrose paired with

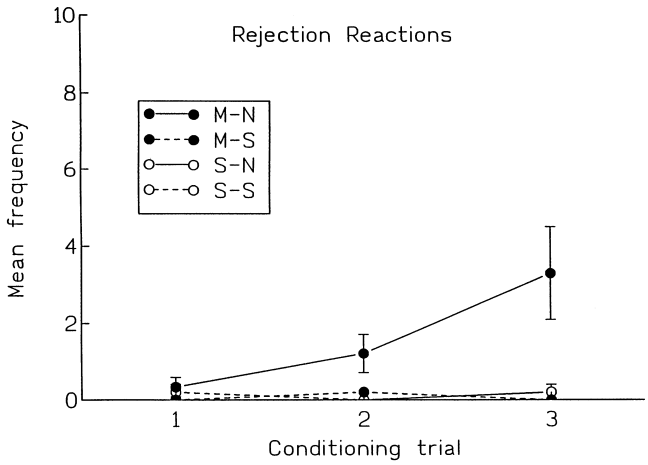

FIG. 1. Mean frequency of rejection reactions displayed by the various groups during TR conditioning trials 1–3 in Experiment 1A.

naloxone-precipitated morphine withdrawal (group M-N) developed active rejection of a flavor with which it was associated. A $2 \times 2 \times 3$ analysis of variance (ANOVA) of the rejection reaction scores, with the between groups factors of presucrose drug (morphine, saline) and postsucrose drug (naloxone, saline) and the within-groups factor of trial (1–3), revealed a significant presucrose drug by postsucrose drug interaction, $F(1, 38) = 17.4$, $p < 0.01$. Subsequent t-tests (with criterion level set at $p < 0.01$, because of multiple comparisons) revealed that group M-N displayed more active rejection reactions during conditioning than did any other group.

Drug-Free TR and Consumption Tests

In contrast with the results of the TR conditioning trials, none of the groups displayed conditioned active rejection reactions during the drug-free TR test, nor conditioned taste avoidance during the drug-free consumption test. Tables 1 and 2 present the mean (±SEM) scores for each group displayed on both tests. A 2×2 between-groups ANOVA of the data from each test summarized in Tables 1 and 2 indicated no significant main effects or interactions. [Two rats drank neither sucrose nor water during the 2-h consumption test (administered in a nonwater deprived state)].

In summary, rats in group M-N displayed active rejection of sucrose solution during conditioning trials (while experiencing the stimulus properties of morphine), but not during the subsequent drug-free test trial. These group M-N rats also failed to display avoidance of the sucrose solution in the consumption test. Results of Experiment 1A indicate that the sucrose had indeed become conditionally unpalatable as a result of its association with naloxone-precipitated withdrawal; however, this rejection of sucrose was apparent only when subjects were injected with morphine prior to the TR test. These results suggested that the conditional rejection of sucrose was state dependent, being seen only when rats were tested in the same pharmacological state in which they had acquired the rejection response. The purpose of Experiment 1B was to evaluate this interpretation.

EXPERIMENT 1B

In phase 1 of Experiment 1B, rats assigned to groups M-N and M-S in Experiment 1A were now tested in the same morphine state in which they had been conditioned. On the basis of a state-dependent learning interpretation of the results of Experiment 1A, we would expect evidence of conditioned aversion to the sucrose solution that had been paired with naloxone-precipitated withdrawal. Phase 2 of Experiment 1B was designed to permit an additional evaluation of the contribution of state dependency to withdrawal-elicited conditioned aversions. Following three additional TR conditioning trials, half the rats in each of groups M-N and M-S were tested in the morphine state, and half in a nondrugged state.

TABLE 1

FREQUENCY OF REJECTION REACTIONS DISPLAYED DURING THE DRUG-FREE TASTE REACTIVITY TEST IN EXPERIMENT 1A

	Presucrose Drug			
	Morphine		Saline	
Postsucrose Drug	Mean	SEM	Mean	SEM
Naloxone	0.2	0.12	0.0	0.00
Saline	0.0	0.00	0.1	0.00

During TR conditioning, the presucrose drug was administered 60 min prior to each TR trial.

TABLE 2

SUCROSE PREFERENCE RATIOS DISPLAYED DURING THE DRUG-FREE CONSUMPTION TEST OF EXPERIMENT 1A

	Presucrose Drug			
	Morphine		Saline	
Postsucrose Drug	Mean	SEM	Mean	SEM
Naloxone	0.84	0.05	0.92	0.03
Saline	0.95	0.02	0.91	0.04

METHOD

Phase 1—Conditioned Rejection Reactions Following Presucrose Morphine Administration

Three days after the drug-free TR and consumption test trials in Experiment 1A, rats in groups M-N and M-S were given an additional 2 min TR test trial followed immediately by a two-bottle consumption trial, with both tests taking place while the rats were in a morphine state. All rats were injected SC with 20 mg/kg morphine 60 min prior to receiving an intraoral infusion of sucrose solution for a 2-min period, and their TR reactions were videotaped. Because they were narcotized and were not water deprived during the consumption trial, few rats drank either sucrose solution or water. The results of the consumption test, therefore, will not be discussed.

Phase 2—State-Dependency of Conditioned Rejection Reactions

Beginning 3 days after the morphine test trials, rats in groups M-N and M-S were given an additional three TR conditioning trials (trials 4–6, with each trial separated by 72 h). These trials were conducted identically to trials 1–3, except that the naloxone injections were administered subcutaneously (SC). The route of administration was changed from IP to SC to increase the efficacy of naloxone, because it has been reported that first pass metabolism reduces bioavailability of IP administered naloxone (8). Because of a loss of cannulae during conditioning trials of Experiment 1B, the final analyses included 10 rats in group M-N and 8 rats in group M-S.

Three days after TR conditioning trial 6, rats in groups M-N and M-S received a 2-min TR test trial for state-dependent learning. Sixty minutes prior to the test trial, half of the rats in group M-N ($n = 5$) and half of the rats in group M-S ($n = 4$) were injected SC with 20 mg/kg of morphine; the remaining rats in group M-N ($n = 5$) and group M-S ($n = 4$) were injected with saline solution. They then received a 2-min intraoral infusion of sucrose solution and their taste reactions were videorecorded.

RESULTS

Phase 1

In this phase, all rats were administered morphine prior to the TR and consumption tests. That is, they were tested in the same drug state in which they were conditioned. In contrast to the tests in Experiment 1A (when rats were tested in a drug-

free state), there was now evidence that M-N group rats displayed aversive reactions to sucrose. The mean number of aversive reactions displayed by rats in group M-N was significantly greater than that displayed by rats in group M-S (mean number of rejection reactions = 2.3 and 0, respectively, $t(20) = 2.2, p < 0.05$).

Phase 2

In this phase, rats initially received three additional TR conditioning trials (i.e., trials 4–6). The mean (±SEM) number of rejection reactions displayed by rats in groups M-N and M-S during these conditioning trials is presented in Fig. 2. During the sucrose infusion, rats in group M-N displayed more rejection reactions across the trials than did rats in group M-S, as revealed by a significant conditioning group by trial interaction, $F(2, 32) = 3.3, p < 0.05$. On both trials 5 and 6, group M-N displayed more active rejection reactions than did group M-S ($ps < 0.05$).

Following the sixth TR conditioning trial, rats again received a TR test. Half of rats assigned to each of groups M-N and M-S were tested following morphine administration, and half were tested following saline administration. A 2 × 2 ANOVA revealed a significant conditioning group by test drug interaction, $F(1, 13) = 65.1, p < 0.01$; group M-N displayed active rejection reaction, but only when tested in the morphine state (mean = 8.0, SEM = 1.9). Those rats in group M-N tested in the drug-free state, as well as rats in group M-S tested in the morphine or drug-free state, all failed to display any active rejection reactions (i.e., zero rejection reactions were observed).

DISCUSSION

Acute naloxone-precipitated morphine withdrawal produced a conditioned sucrose aversion in Experiment 1, but that aversion was expressed only when the same morphine stimulus state present during conditioning was also present during testing. During the course of these conditioning trials (trials 1–3 in Experiment 1A and trials 4–6 in Experiment 1B), rats in group M-N developed conditioned rejection of sucrose solution; during each of these trials, rats in group M-N were administered morphine 60 min prior to the sucrose infusion. During subsequent drug-free TR test trials (after three conditioning trials in Experiment 1A and after a total of six conditioning trials in Experiment 1B), rats in group M-N did not display these conditioned rejection reactions. However, when rats were administered the test trial following a morphine injection, they displayed the rejection reactions that were evident during conditioning trials. The pattern of results suggests that the display of a naloxone-withdrawal elicited conditioned sucrose aversion is state dependent.

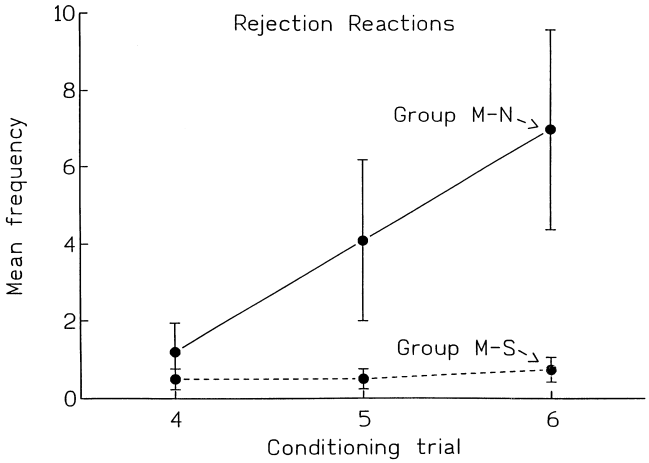

FIG. 2. Mean frequency of rejection reactions displayed by Group M-N and M-S during Phase 2 TR conditioning trials 4–6 in Experiment 1B.

EXPERIMENT 2

In Experiments 1A and 1B, morphine was administered 60 min prior to each of the TR conditioning trials. The results of these experiments suggested that naloxone-precipitated withdrawal from this opiate did elicit conditioned rejection reactions, but the display of these learned responses was morphine state dependent. That is, they were seen in morphine-pretreated rats, but not in saline-pretreated rats. Experiment 2 was designed to evaluate the ability of naloxone-precipitated withdrawal from acutely administered morphine to produce a taste aversion in the absence of a salient morphine cue during conditioning.

Although precipitated withdrawal was elicited 60 min after morphine administration in Experiments 1A and 1B, there is evidence that such withdrawal responses can be observed when an opioid antagonist is administered long after a single dose of morphine [e.g., (2,9,12,23)]. Humans (7,9) and rats (2) remain sensitive to the precipitated withdrawal effects of naloxone up to 24 h after a single morphine injection, even though the physiological, behavioral, and subjective effects of morphine are no longer apparent at this time (2,7,9). In Experiment 2, we examined the ability of morphine withdrawal to produce a conditioned sucrose aversion when naloxone was administered 1 day after morphine.

METHOD

The subjects were 27 male Sprague–Dawley rats weighing between 274–364 g on the first conditioning trial. They were treated in a manner similar to those of Experiment 1 except as indicated.

On each of three TR conditioning trials (separated by 72 h), rats were injected SC with 20 mg/kg of morphine. The next day (22 h later), they received an intraoral infusion of 17% sucrose solution in the TR chamber. Immediately following the sucrose infusion, rats were injected SC with either 1 mg/kg of naloxone or saline. Thus, as in Experiment 1A , there were four groups: M-N ($n = 8$), group M-S ($n = 7$), group S-N ($n = 6$), group S-S ($n = 6$). However, in the present experiment there was a 22-h interval (rather than a 1-h interval) between the pre- and postsucrose injections.

Three days after the final conditioning trial, the rats received a TR test trial during which they were infused with sucrose solution in the same manner as during conditioning, but without prior treatment with morphine. A sucrose preference test was initiated immediately following the TR test trial. Rats were returned to their home cages, which were equipped with two bottles—one containing a 17% sucrose solution, and one containing tap water, for 24 h and the amounts consumed were measured.

RESULTS AND DISCUSSION

Naloxone-precipitated withdrawal produced a taste aversion even when naloxone was administered 22 h after 20 mg/

kg of morphine. Figure 3 presents the mean frequency of rejection reactions displayed by each group during conditioning trials 1–3 in Experiment 2. A 2 × 2 × 3 mixed factors ANOVA of the rejection reaction scores, with the between-groups factors of presucrose drug (morphine or saline) and postsucrose drug (naloxone or saline) and the within-groups factor of conditioning trial, revealed a significant presucrose drug by postsucrose drug interaction, $F(1, 23) = 4.7$, $p < 0.05$. Rats in group M-N displayed more rejection reactions than did rats in any other group ($ps < 0.05$).

Acute naloxone-precipitated withdrawal produced conditioned sucrose rejection in the TR test and conditioned sucrose avoidance in the consumption test. A 2 × 2 ANOVA revealed a significant presucrose drug by postsucrose drug interaction, $F(1, 23) = 5.1$, $p < 0.05$; group M-N displayed rejection reactions (mean = 6.0, SEM = 2.0), while groups M-S, S-N, and S-S failed to display any rejection reactions.

Rats in group M-N also displayed a significant conditioned sucrose avoidance in the 24-h two-bottle consumption test. Figure 4 presents the mean (±SEM) sucrose preference ratios for the various groups in Experiment 2. A 2 × 2 between groups ANOVA revealed a significant presucrose drug by postsucrose drug interaction, $F(1, 23) = 8.2$, $p < 0.01$. Group M-N displayed a lower mean sucrose preference ratio than any other group ($ps < 0.05$).

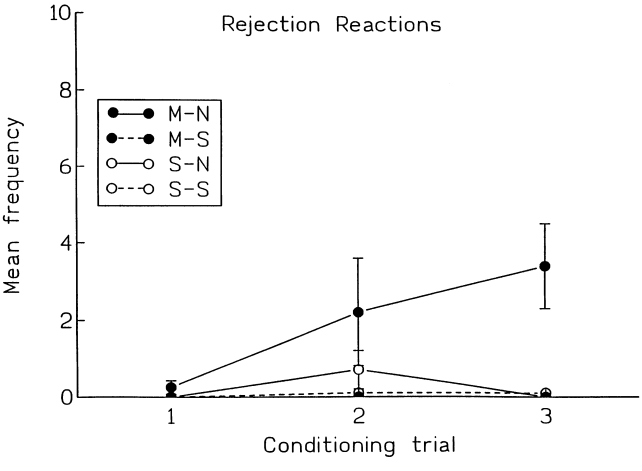

FIG. 3. Mean frequency of rejection reactions displayed by the various groups during the TR conditioning trials in Experiment 2 with a 22-h interval between morphine and naloxone-precipitated withdrawal.

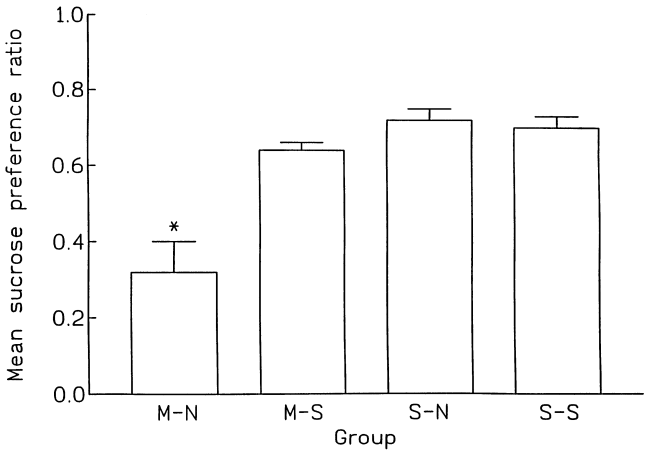

FIG. 4. Mean sucrose preference ratios during the 24 h consumption test for the various groups in Experiment 2. *$p < 0.05$.

GENERAL DISCUSSION

Withdrawal from acutely administered morphine produced conditioned rejection of sucrose solution. The results of these experiments indicate that acute naloxone-precipitated withdrawal produces an aversive effect that is capable of becoming associated with a flavor. The results also have implications for state-dependent learning of withdrawal-elicited aversions.

Although conditioned changes in the palatability of sucrose were established across conditioning trials in Experiment 1A when morphine preceded TR conditioning by 1 h, these changes were not apparent during drug-free testing. A state-dependent learning interpretation of the results of Experiment 1A was confirmed by the results of Experiment 1B. In Experiment 1B, rats displayed a conditioned sucrose aversion when tested in the same state experienced during conditioning (morphine state), but not when tested in a different state (drug-free state). It is apparent that the morphine state served as a discriminative signal that sucrose was aversive; in the absence of the morphine signal, sucrose was not aversive. Drug-discriminated taste avoidance learning has been reported with drug cues of morphine (13), naloxone (10), and phencyclidine (14). In the drug-discrimination paradigm, rats are given explicit training, during which exposure to a flavor is preceded by an injection of a drug, and followed with an injection of an emetic agent such as lithium chloride. On alternate days, rats are exposed to the flavor in a drug-free state, and are able to consume it with no aversive consequences. Rats quickly (14) learn to withhold consumption of the flavored solution in the drug state, and to consume the flavored solution in the drug-free state. Our results suggest that even without such explicit discrimination training, the morphine state effectively serves as a cue to signal taste aversion using the TR paradigm. In Experiment 1A, our procedure provided no opportunity for the drug to differentially predict that the taste would be followed by aversive consequences, yet the rats displayed a taste aversion only when tested in the state in which they learned the aversion, and not in the absence of this state. The taste aversion was measured by the test of palatability, the taste reactivity test. These results suggest that a drug state can signal the perceived palatability of a taste.

When the morphine state did not serve as a cue during conditioning (Experiment 2), naloxone-precipitated withdrawal from acute morphine produced a conditioned sucrose aversion that was readily apparent in a drug-free test. In Experiment 2, naloxone-precipitated withdrawal was induced 22 h after acutely administered morphine. With a 22 h interval, the stimulus properties of morphine were dissipated at the time of the TR conditioning trials (2,7,9), but naloxone was still capable of precipitating withdrawal from acutely administered morphine.

Naloxone has been shown to produce taste avoidance in drug discrimination studies (10), although the failure to see aversive conditioning in the S-N groups suggests that naloxone alone was not aversive in the present experiments. Furthermore, a dose of naltrexone as high as 10 mg/kg does not produce conditioned rejection reactions (19). Although the results suggest that aversions developed to a taste paired with

precipitated withdrawal, it remains possible that the administration of morphine is acting to enhance a subthreshold aversion induced by naloxone.

Naloxone-precipitated withdrawal clearly has the capacity to produce conditioned taste avoidance in rats that are chronically pretreated with morphine (3,11,15,16,20,21,23). The results of the consumption test of Experiment 2 indicate that morphine withdrawal also produces taste avoidance in nondependent rats that are acutely pretreated with morphine 22 h prior to receiving naloxone. Additionally, we report that the conditioned taste avoidance produced by naloxone-precipitated withdrawal appears to be mediated by a shift in the palatability of the taste. Rats display conditioned rejection of sucrose that is paired with naloxone precipitated withdrawal from 20 mg/kg morphine whether the morphine was administered 1 h or 22 h prior to naloxone.

The results of these experiments demonstrated that withdrawal from a dose of 20 mg/kg morphine, precipitated by 1 mg/kg of naloxone, produced a taste aversion. Other investigators have used suppression of operant responding as an index of opiate withdrawal [e.g., (1,5)], and have reported that withdrawal effects may be seen with smaller doses of antagonist and agonist, for example, .25 mg/kg naloxone administered 48 h after 10 mg/kg morphine (5). In view of this, it would be of interest to examine the effects of a wider range of agonist and antagonist doses in the TR paradigm, particularly with reference to the apparent state dependency of the taste aversions seen in Experiments 1A and 1B.

The present findings suggest that while the precipitated withdrawal experience is aversive, learned associations with this aversive event may or may not affect future behavior, depending on the intensity of the drug-state stimuli present at the time of learning. These results may have relevance to the development of effective treatments for addiction, where learning processes have been shown to play an important role. The taste reactivity test provides a useful measure of the aversive properties of morphine withdrawal.

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