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Rewarding and Aversive Effects of Morphine: Temporal and Pharmacological Properties[1]

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SHERMAN, J. E., C. PICKMAN, A. RICE, J. C. LIEBESKIND AND E. W. HOLMAN. *Rewarding and aversive effects of morphine: Temporal and pharmacological properties.* PHARMAC. BIOCHEM. BEHAV. 13(4) 501–505, 1980.—To assess morphine-induced location preferences and flavor aversions, rats were administered morphine sulfate (10 mg/kg, IP) either immediately before (Experiment 1) or immediately after (Experiment 2) confinement for 20 min in one side of a shuttlebox with access to a flavored solution. On control trials the rats were administered saline and confined for 20 min on the opposite side with a differently flavored solution. In subsequent choice tests, it was found that morphine injections before confinement produced a preference for the side associated with morphine and indifference to the flavors, whereas morphine injections after confinement produced an aversion to the flavor paired with morphine and indifference to the sides. Experiments 3 and 4, using a procedure similar to that of Experiment 1, showed that naloxone (1 mg/kg, IP) blocked the morphine-induced side preference, although given alone it was without effect in this test.

Conditioned flavor aversion Conditioned location preference Reinforcement Selective association
Rats Morphine Naloxone

MORPHINE is reported to have both rewarding and aversive properties. Evidence of its rewarding effects comes from a variety of experimental situations. Animals self-administer morphine through intravenous [8, 9, 12, 37], intraventricular [1,2] and oral [13, 26, 32, 34] routes. They prefer a location associated with morphine administered systemically [18, 19, 25, 30, 32] or intracranially [25], and they increase their running speed through a straight alley when morphine is administered in the goal box [38]. On the other hand, the aversive effects of morphine are demonstrated by the development of a flavor aversion after pairing a novel flavor with morphine administration [3, 4, 5, 10, 14, 17, 20, 21, 27, 29, 36, 38].

White *et al.* [38] demonstrated that rats trained to run down a straight alley for food in a goal box increased running speed when morphine was subsequently given in the goal box even though they concurrently developed an aversion to the food. This finding shows that the same dose of morphine can have both rewarding and aversive effects in the same subjects and hence calls into question the widely held notion that a stimulus is unitary in its reinforcing properties.

The present study sought to investigate the rewarding and aversive properties of morphine in rats employing a procedure used previously to analyze these properties of amphetamine [28,31]. With this procedure, on some days rats are placed in one distinctive compartment of a two-compartment shuttlebox with a distinctive flavor concurrently available. On other days the rats are placed in the second compartment with a different flavor present. One side of the shuttlebox and one flavor are consistently paired with administration of the drug of interest, here morphine, the other side and flavor with physiological saline. Following training, location and flavor preference tests are conducted separately. This procedure is designed to reveal both morphine's rewarding effects (indicated by a preference for the location paired with the drug) and its aversive effects (indicated by an aversion for the drug-associated flavor).

In the present study, a temporal analysis of the rewarding and aversive properties of morphine was conducted; morphine was administered either before rats were exposed to the location and taste cues (Experiment 1) or after they were exposed to these cues (Experiment 2). Additionally, it was determined whether the rewarding effects of morphine could be blocked by the opiate antagonist naloxone (Experiment 3) and whether naloxone alone directly affected location and flavor cue preferences (Experiment 4).

EXPERIMENTS 1 AND 2

METHOD

Subjects

The subjects in each experiment were 12 female Sprague-Dawley rats obtained from Simonsen Labs in Gilroy, CA. The rats were 90–120 days old at the start of the experiments and were maintained at 85% of their free-feeding weight.

Apparatus

Each rat was trained in a rectangular Plexiglas shuttlebox (72.5×31×28 cm) with a stainless-steel grid floor and a re-

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movable Plexiglas barrier that restricted rats to the appropriate side of the shuttlebox during training periods. Light gray cardboard behind the transparent Plexiglas walls and between the 2-sided Plexiglas barrier faced the interior of the right side of the shuttelbox. Vertical stripes of 2 cm wide black tape, 2 cm apart, were on the white cardboard facing the interior of the left side of the shuttlebox and on the left side of the otherwise transparent Plexiglas roof. Vertical strips of transparent, 0.6 cm thick and 2 cm wide Plexiglas were superimposed on the interior of the left side of the shuttlebox over the white stripes. Thus, the sides differed both visually and tactually. One such shuttlebox was used in Experiments 1 and 3, and two were used in Experiments 2 and 4. The room containing the shuttleboxes was illuminated by a 40 W light bulb covered with red transparent plastic.

There were two drinking solutions: the HCl solution contained 0.1% HCl and 5% sucrose, and the NaCl solution contained 3% NaCl and 5% sucrose. They were presented to the rats in graduated test tubes with drinking spouts. A small hole centered on each end of the shuttlebox 9 cm above the grid floor, through which the drinking spout was placed, allowed the rats access to a flavored solution during training.

The morphine and saline injections contained, respectively, 10 mg/kg morphine sulfate in isotonic saline, and isotonic saline alone; injections were administered intraperitoneally (IP) in a volume of 2 ml/kg.

Procedure

The rats were housed in individual cages under conditions of constant temperature, constant illumination, and unlimited access to water. On each of three days before the first training day, the rats were given 20 ml of 5% sucrose solution in their home cages in order to reduce possible neophobic reactions to the solutions presented on the training days. The drug schedule during training consisted of six presentations of saline and six of morphine; saline on Mondays and Thursdays and morphine on Tuesdays and Fridays. On the other days, the rats remained in their home cages. The rats were tested on the Sunday following the last presentation of morphine.

On training days, the rats received a distinctive set of cues associated with either the morphine or saline injection. On saline days, each rat was placed in one side of the shuttlebox for 20 min with access to 30 ml of either the NaCl solution or HCl solution. On morphine days, each rat was placed in the opposite side of the shuttlebox for 20 min with access to the other solution. Experiments 1 and 2 differed in the interval between injection and placement in the box. In Experiment 1 the rats were given their injections immediately before they were placed in the shuttlebox; in Experiment 2 they were injected immediately after being removed from the shuttlebox. Thus, in contrast to the rats in Experiment 1, those of Experiment 2 never experienced the sequelae of morphine injection in the shuttlebox.

In both experiments, half the rats in each group were placed in the left side of the shuttlebox on morphine days and half in the right side, and half the rats in each group received HCl solution on morphine days and half received NaCl solution. In Experiment 2, half the rats in each group were trained and tested in one shuttlebox and half in the other.

On the test day, acquired side and flavor preferences were assessed. First, each rat was placed in the middle of the shuttlebox without the barrier, allowing access to both sides, but no solutions were provided; the rat's location was automatically recorded for 20 min. Immediately after the side preference test, the rat was returned to its home cage and offered 30 ml each of the HCl and the NaCl solutions in adjacent test tubes, for 20 min; total consumption of each solution was recorded.

Statistical Analyses

All statistical tests were conducted with the analysis of variance. For flavor, the dependent variable was amount consumed; the within-subject factor was flavor (HCl vs NaCl); the between-subject factor was reinforced cue (morphine with HCl vs morphine with NaCl). For location, the dependent variable was time spent on the left side; the between-subject factors were reinforced cue (morphine with left side vs morphine with right side), and shuttlebox (in Experiment 2). The rejection criterion was $p<0.05$.

RESULTS

For both Experiments 1 and 2, Table 1 presents the consumption of each solution averaged across all training days, the average consumption of each solution during the flavor choice test, and the average time spent in each side of the shuttlebox during the location preference test. These data are presented in terms of the flavor or location cue paired with morphine or saline injection.

During training there was no evidence for the development of an aversion to the flavor paired with the morphine injection in either experiment. Rats drank a comparable amount of the morphine and saline solutions across all six pairs of training days. Statistical analyses of the training data failed to yield a significant effect of drug (morphine vs saline) in Experiment 1 ($F<1$) or Experiment 2, $F(1,10)=3.21$. However, the results of the more sensitive two-bottle preference test [15] revealed a statistically significant aversion to the morphine-paired flavor in Experiment 2, $F(1,10)=7.79$, but not in Experiment 1 ($F<1$). In contrast to the flavor preference results, the location test revealed a statistically significant preference for the morphine-paired side in Experiment 1, $F(1,10)=10.53$, but not in Experiment 2 ($F<1$).

DISCUSSION

Rats injected with morphine immediately *before* a 20 min exposure to a flavor and location compound (Experiment 1) exhibited a location preference but no evidence of a flavor aversion. In contrast, rats injected immediately *after* exposure to these compound cues (Experiment 2) showed a flavor aversion but no evidence of a location preference. These results show that (1) only the flavor cue became aversive and the location cue preferred and (2) the temporal relationship between drug administration and exposure to the flavor and location compound selectively favored either the conditioning of the morphine-induced flavor aversion or location preference.

This study confirms previous reports showing that a flavor cue paired with morphine yields a conditioned aversion [3, 4, 5, 10, 14, 17, 20, 21, 27, 29, 36, 38] whereas a location cue paired with morphine results in a conditioned preference [18, 19, 25, 30, 32]. Moreover, these results, along with those of White *et al.* [38] show that such effects can be demonstrated in a single experimental context. Clearly, flavor and location cues become selectively associated with different morphine effects. Whereas a similar selective association has been demonstrated with amphetamine reinforcement [28,31], alcohol reinforcement has been found to produce conditioned aversions to both flavor and

TABLE 1

MEAN CONSUMPTION OF FLAVORS ASSOCIATED WITH EACH DRUG IN TRAINING AND TESTING AND MEAN TIME SPENT IN LOCATION ASSOCIATED WITH EACH DRUG IN TESTING FOR EXPERIMENTS 1 AND 2

Experiment		Drug: Morphine	Drug: Saline
1 (Drug before cue)	Flavor in training	6.2 ml	6.1 ml
	Flavor in test	7.0 ml	4.9 ml
	Location test	11.8 min	8.2 min
2 (Drug after cue)	Flavor in training	9.6 ml	7.6 ml
	Flavor in test	4.3 ml	8.6 ml
	Location test	9.7 min	10.3 min

TABLE 2

MEAN CONSUMPTION OF FLAVORS ASSOCIATED WITH EACH DRUG IN TRAINING AND TESTING AND MEAN TIME SPENT IN LOCATION ASSOCIATED WITH EACH DRUG IN TESTING FOR EXPERIMENTS 3 AND 4

Experiment		Drug: Morphine	Drug: Morphine & Naloxone
3	Flavor in training	6.3 ml	3.4 ml
	Flavor in test	7.0 ml	5.8 ml
	Location test	11.5 min	8.5 min
Experiment		Naloxone	Saline
4	Flavor in training	2.4 ml	3.4 ml
	Flavor in test	2.8 ml	3.3 ml
	Location test	9.7 min	10.3 min

location cues paired with the drug [7]. Thus, all common drugs of abuse do not necessarily yield the same pattern of selective associations, at least at the doses so far studied.

The absence of a conditioned flavor aversion when morphine was administered before presentation of the flavor cue (Experiment 1) is not surprising. Coussens, Crowder and Davis [6] also failed to observe a morphine-conditioned flavor aversion when the flavor cue was presented only 1 min before morphine administration and remained available afterward. All reported demonstrations of morphine-conditioned flavor aversions have employed procedures in which the flavor preceded drug administration by at least 10 min [3, 4, 5, 10, 14, 17, 20, 21, 27, 29, 36, 38]. This pattern of results is consistent with Logue's [22] generalization that the acquistion of a drug-induced conditioned flavor aversion is strongest when the flavor precedes rather than follows administration of the drug. Nevertheless, amphetamine has been shown to produce both flavor aversions and location preferences when drug administration has preceded the flavor by as much as 2 hr [28,31]. Thus, the absence of an aversion when morphine was administered before the flavor does not reflect a general characteristic of drugs that have rewarding effects.

The absence of a morphine-conditioned location effect when the drug was administered *after* exposure to the location cue (Experiment 2) is also not unprecedented. Kumar [19] found that rats preferred a location cue repeatedly paired with a high dose of morphine (120 mg/kg) when drug administration immediately preceded 30 min exposure to the location but not when drug administration followed exposure to the location cue by 3–5 min. Thus, as in the present study in which a much lower dose of morphine was administered (10 mg/kg), a location preference was only observed when location cues were simultaneous with drug action; when location cues preceded but did not accompany drug action no location preference was observed. It appears that temporal contiguity of location cues and the sequelae of morphine administration is a necessary condition for showing morphine-conditioned location effects.

As Kumar [19] suggested, the morphine-induced location preference in his study was most likely mediated by the alleviation of withdrawal symptoms. In contrast, the procedures of the present study minimized the development of opiate dependence and hence a more direct reinforcing action of morphine is implicated. This was accomplished by using the same low dose of morphine (10 mg/kg) as employed by others to condition a location preference [25, 30, 32]. However, in any study involving more than one injection of morphine the possibility of dependence cannot be eliminated.

The present findings confirm and extend those of White *et al.* [38] demonstrating the "paradoxical" nature of morphine reinforcement. They found that rats trained to run down a straight alley for food in the goal box showed an increase in running speed when morphine (9 or 15 mg/kg, IP) was subsequently given in the goal box even though a concurrent flavor aversion to the food developed. One distinction between the White *et al.* study and the present one is that they simultaneously observed the aversive and rewarding effects of morphine in a single experiment, whereas we observed these effects across two experiments differing only in the temporal relationship between morphine administration and exposure to the compound flavor and location cues. In the present experiments a taste aversion developed only when the flavor cue preceded morphine administration, but a location preference occurred only when the location cue followed drug administration. Interestingly, the experiment of White *et al.* [38] included both these temporal relationships within the same procedure. Their rats had access to food in the goal box for 10 min before morphine injection, and then were returned to the empty goal box for another 50 min after injection. Thus, flavor cues preceded morphine administration and location cues (the goal box) followed morphine administration, the very conditions our experiments suggest are necessary for demonstrating both the aversive and rewarding effects of morphine.

EXPERIMENTS 3 AND 4

Opiate antagonists have been shown to attenuate the reinforcing effects of morphine. LeBlanc and Cappell [21] and Van der Kooy and Phillips [36] found that naloxone partially attenuates morphine-induced conditioned flavor aversions, implicating some role for mediation by naloxone sensitive opiate receptors. Experiment 3 sought to extend these findings by addressing whether the morphine-induced location preference observed in Experiment 1 would also be attenuated by naloxone.

In Experiment 3 morphine was consistently paired with one side of the shuttlebox, whereas morphine plus naloxone were paired with the other side. It was anticipated that if naloxone attenuated the reinforcing effect of morphine in this situation, a conditioned preference for the side paired with morphine alone would develop. Experiment 4 tested whether naloxone alone would produce a conditioned location effect. Here, naloxone was paired with one side of the shuttlebox, saline with the other. For both Experiments 3 and 4, a distinctive flavor cue was presented in compound with each side of the shuttlebox as in Experiments 1 and 2.

METHOD

Subjects

The subjects in each experiment were 12 female Sprague-Dawley rats maintained at 85% of their free-feeding weight. All other subject-related information is as previously described.

Apparatus

The apparatus was the same as previously described.

Procedure

In Experiment 3 morphine injections contained 10 mg/kg of morphine sulfate in isotonic saline; the morphine plus naloxone injection contained 10 mg/kg of morphine sulfate and 1 mg/kg of naloxone hydrochloride in isotonic saline. In Experiment 4 the naloxone and saline injections contained respectively 1 mg/kg of naloxone hydrochloride in isotonic saline, and isotonic saline alone. The volume of all injections was 2 ml/kg.

The procedure followed that of Experiment 1 except that different drugs were administered. The drug schedule during training for Experiment 3 consisted of six injections of morphine alone, on Mondays and Thursdays, and six of morphine plus naloxone, on Tuesdays and Fridays. For Experiment 4 the drug schedule was six injections of naloxone, on Mondays and Thursdays, and six injections of saline, on Tuesdays and Fridays.

On training days, the rats received a distinctive set of location and flavor cues associated with each of the two kinds of injections in Experiment 3 (morphine vs morphine plus naloxone) and Experiment 4 (naloxone vs saline). In both experiments the rats were injected immediately before a 20 min exposure to the compound location and flavor cues. Testing for possible conditioned location and flavor effects was conducted as described in Experiment 1. Statistical analyses were the same as in Experiments 1 and 2.

RESULTS

For both Experiments 3 and 4, Table 2 presents the consumption of each solution averaged across all training days, the average consumption of each solution during the flavor choice test, and the average time spent in each side of the shuttlebox during the location preference test.

During training the rats in Experiment 3 drank significantly more of the flavor paired with morphine than the flavor paired with morphine plus naloxone, $F(1,10)=24.74$. In Experiment 4 there was less consumption of the naloxone paired flavor than the saline paired flavor in training but this difference only approached statistical significance, $F(1,10)=3.38$, $0.05<p<0.1$.

The results of testing failed to yield a significant difference in flavor consumption in either experiment ($Fs<1$). However, the location test indicated that in Experiment 3 rats spent significantly more time on the side paired with morphine than the side paired with morphine plus naloxone, $F(1,10)=5.24$. In Experiment 4, rats showed no preference between the naloxone- and saline-paired sides ($F<1$).

DISCUSSION

Experiment 3 demonstrated that rats spent more time in the side paired with morphine than the side paired with morphine plus naloxone. The location test results of Experiment 4 suggest that naloxone alone does not promote a conditioned location effect. Consequently, it is unlikely that the preference for the morphine associated location in Experiment 3 is due to the conditioning of an aversion by the naloxone itself. There remain two possible, but not necessarily exclusive, explanations for the influence of naloxone in Experiment 3. First, naloxone may have simply blocked the rewarding effects of morphine, suggesting that such rewarding effects are mediated by naloxone sensitive opiate receptors. Second, to the extent that opiate dependence developed in the morphine-injected rats, naloxone may have precipitated withdrawal and hence conditioned an aversion to the side paired with morphine plus naloxone. The present experiments do not discriminate between these possibilities.

Since the temporal parameters of Experiment 1 did not promote a morphine-conditioned taste aversion, it was not surprising that in Experiment 3, which used the same parameters, a flavor aversion also was not seen. Similarly, in Experiment 4 naloxone alone did not produce a flavor aversion. However, with more favorable temporal parameters, naloxone has been shown to support a conditioned flavor aversion with the dose used here [34].

The results of Experiment 3 indicated that during training morphine plus naloxone acutely suppressed consumption compared to morphine alone. This suppression is consistent with the possibility, mentioned above, that the naloxone may have precipitated withdrawal during training, although no other behaviors characteristic of withdrawal were observed (such as hyperactivity, 'wet dog' shakes, teeth chattering, facial tremors, or diarrhea). In Experiment 4 naloxone alone did not significantly suppress consumption but the direction of the result is consistent with numerous reports showing naloxone at the same or lower dose can, in fact, acutely suppress food and water consumption [11, 16, 23, 24, 33]. The absence of a significant difference here may be attributed to the numerous procedural differences between the present study and those finding a significant effect, or to the relatively low baseline of consumption on saline days, which may have obscured the detection of naloxone's suppressive effects.

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