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Morphine preexposure facilitates morphine place preference and attenuates morphine taste aversion

Gregory R. Simpson[a,*], Anthony L. Riley[b]

[a]*Department of Psychology, University of Miami, 5665 Ponce de Leon Blvd Coral Gables, FL, 33146-0751, USA*
[b]*Psychopharmacology Laboratory, Department of Psychology, American University Washington, DC 20016, USA*

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Abstract

Repeated morphine preexposure has been reported to enhance measures of morphine reward (conditioned place preference; CPP) and attenuate measures of morphine aversion (conditioned taste aversion; CTA). These effects are generally independently assessed, limiting the ability to determine if the enhancing and attenuating effects of morphine exposure are mediated by a common factor. To assess any potential relationship between these two effects, the present study examined the impact of morphine preexposure on these motivational properties of morphine using a combined CTA/CPP procedure in which the same animals receive concurrent taste and place conditioning. Specifically, male Sprague–Dawley rats were preexposed to morphine [5 mg/kg; subcutaneously (sc)] or equivolume drug vehicle. Following preexposure, animals were given saccharin to drink and injected with morphine sulfate (1 or 5 mg/kg sc) or drug vehicle (CTA). Immediately thereafter, they were placed on one side of a two-compartment chamber (CPP). On the next day, they were given water followed by injections of the drug's vehicle and then placed in the other compartment. There were four such conditioning cycles after each of which a CTA and CPP test were given. While preexposure to morphine attenuated morphine-induced CTAs, morphine-induced CPPs were enhanced within the same animals. These effects of morphine preexposure were dose- and time-dependent and parallel. These data indicate that the attenuating and sensitizing effects of morphine preexposure on taste aversions and place preferences, respectively, could be mediated by a common mechanism, although other possibilities for these effects of morphine preexposure remain.

Keywords: Morphine; Drug preexposure; Reward; Aversion; CTA; CPP

1. Introduction

The effects of morphine are well documented to be influenced by repeated administration (Stewart and Badiani, 1993). Whereas some effects, such as locomotor activity (Babbini and Davis, 1972; Babbini et al., 1975) or psychomotor activation (Bartoletti et al., 1983), are enhanced with morphine exposure (behavioral sensitization), other effects, such as analgesia (Fabian et al., 2003; Ferguson et al., 1969), are attenuated after such a drug history. Interestingly, investigations of the effects of morphine exposure on morphine's motivational properties have produced both enhancement and attenuation, the direction of the change dependent on the particular affective response being investigated. While repeated exposure to morphine has been shown to *attenuate* the production of a morphine-induced conditioned taste aversion (CTA) (Hunt et al., 1985; LeBlanc and Cappell, 1974; Riley et al., 1976; for review see Riley and Simpson, 2001), a measure of the aversive effects of a drug (LeBlanc and Cappell, 1974; though see Grigson, 1997), such exposure has been shown to *enhance* the acquisition of a morphine-induced conditioned place preference (CPP) (Gaiardi et al., 1991; Lett, 1989; Shippenberg et al., 1996), a measure of drug reward (van der Kooy, 1987; Bozarth, 1987).

Although there have been several mechanisms proposed for the attenuation of morphine-induced taste aversions

* Corresponding author. Tel.: +1 305 243 2029; fax: +1 305 284 4795.
E-mail address: gregorysimpson@miami.edu (G.R. Simpson).

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after repeated morphine exposure, most suggest a decrease in the aversive properties of morphine with such preexposure (e.g., tolerance; Riley et al., 1984; see Riley and Simpson, 2001 for a review). Conversely, enhanced conditioned place preferences observed after morphine exposure have traditionally been explained by an increase in the drug's rewarding effects (e.g., sensitization; Gaiardi et al., 1991; Lett, 1989; Shippenberg et al., 1996). Although these are viable explanations, other possibilities are equally likely. While the CPP and CTA designs are thought to be relatively selective for assessing specific motivational properties (i.e., CPP measures drug reward; CTA measures drug aversion) (see Stefurak et al., 1988), it is possible, for instance, that enhanced CPPs after repeated morphine exposure are related to the aversive properties of morphine. That is, if a decrease in morphine's aversive properties occurs with drug exposure, the drug's overall perceived reinforcing value might increase, which, in turn, may be reflected as an enhanced place preference. Conversely, attenuated CTAs after morphine preexposure might be the result of an increase in morphine's rewarding properties, an effect that decreases its overall perceived aversiveness. Traditional assessments of the effects of morphine preexposure on morphine-induced CPP and CTA, however, have been done independently and under varying parametric conditions, and, consequently have provided no unequivocal evidence suggesting these effects are the result of the same or independent mechanisms.

A concurrent measure of both drug reward and aversion might provide a means of assessing whether or not these underlying processes are separate and/or the extent to which either of these mechanisms (i.e., increased reward or decreased aversion) accounts for the effects of morphine preexposure on both conditioned aversions and preferences. Although there have been several attempts to assess simultaneously drug reward and aversion in the same animals, at the same time and under identical parametric conditions (see Brockwell et al., 1991; Martin et al., 1988; Reicher and Holman, 1977; Sherman et al., 1980; Wise et al., 1976), there are few such attempts examining the effects of drug preexposure on these opposite motivational properties. Specifically, in a report by Martin and his colleagues (Martin et al., 1988) using a combined CTA/CPP design, animals were given five (once every two days) injections of morphine (5 mg/kg; sc) prior to morphine conditioning. There were two conditioning trials, each of which consisted of the presentation of a novel saccharin solution followed by either an injection of morphine (5 mg/kg) or drug vehicle. After each of these injections, the animals were placed into one of two distinctive compartments (the animals were placed into the other compartment the next day after a drug vehicle injection). On the day following the last conditioning trial, animals were tested for their aversion to saccharin (CTA) and their preference for the morphine-associated chamber (CPP). On this day, the animals were given access to both water and saccharin and their fluid consumption was assessed using a two-bottle test. Immediately after this CTA test, the animals were given access to both compartments of the CPP chamber in a drug-free state in order to assess the amount of time spent in the compartment that was paired with morphine injections. Interestingly, although there was a significant attenuation of the morphine-induced CTA with morphine preexposure, there was no alteration of the morphine-induced CPP. Given that aversions and preferences were differentially affected by morphine preexposure, they concluded that the mechanisms underlying the effects of the preexposure on the acquisition of morphine-induced taste aversions and place preferences were independent.

Although the lack of evidence for enhanced place preferences after morphine preexposure is suggestive that the mechanism mediating an attenuated taste aversion is independent of that enhancing conditioned place preferences, it is possible that an increase in the rewarding effects of morphine had occurred in the Martin et al. (1988) report but was not detected. Such an increase can be evidenced in a number of ways. For example, it can be evidenced by a shift in the dose necessary to condition a place preference. Specifically, following morphine preexposure doses generally not effective in conditioning a preference can now successfully establish one (see Lett, 1989).This assessment was not possible in the Martin et al. study, given that only one dose of morphine (5 mg/kg) was used to condition the place preference. That is, there were no data provided demonstrating that this dose was ever ineffective (which would have allowed for an assessment of a change in its effectiveness after preexposure). An increase in the rewarding effects of morphine can also be evidenced by an increased rate in the acquisition of CPPs (see Gaiardi et al., 1991; Shippenberg et al., 1996). Although Martin et al. (1988) used two drug-place pairings in order to condition a place preference, they had only one assessment of this place preference, which occurred after the second trial. Under this condition, both morphine and vehicle-preexposed subjects acquired a CPP. Without an assessment of place preferences after the first conditioning trial, there was no way of determining whether preexposure facilitated acquisition of the place preference. It may well have been the case that after one conditioning trial the group of animals that had been preexposed to morphine demonstrated a preference, whereas, the other group did not (or displayed differing degrees of preference). Therefore, it remains unclear whether there was no change in the rewarding effects of morphine with such preexposure. As such, it is unknown whether aversions and preferences were affected concurrently or in a parallel manner by morphine preexposure.

The present experiment directly assessed the relationship between changes in morphine-induced CTAs and CPPs following chronic morphine exposure. Specifically, animals were preexposed to either morphine (5 mg/kg) or drug vehicle and examined in the aforementioned combined CTA/CPP procedure. They were conditioned with 1

or 5 mg/kg of morphine (to determine if preexposure shifted the dose–response curve to the left) and were assessed for the production of CTAs and/or CPPs after each of the multiple training trials (to determine any shift in the onset of morphine's reinforcing effects with drug preexposure). This procedure allowed for a comprehensive and concurrent assessment of the relationship between any development of enhanced place preferences and attenuated taste aversions.

2. Method

2.1. Subjects

The subjects were 48 male Sprague–Dawley rats, approximately 8 weeks of age and 250 g in weight. Guidelines established by the Institutional Animal Care and Use Committee at American University were followed at all times.

2.2. Apparatus

Subjects were housed individually in stainless-steel wire cages with *ad-lib* access to food and water. They were maintained on a 12:12 light:dark cycle (lights on at 0800 h) and at an ambient temperature of 23 °C for the duration of the experiment. Graduated 50-ml Nalgene centrifuge tubes were attached to the front of the cages to provide 20-min access to water or saccharin.

The place conditioning apparatus consisted of four separate shuttle-box chambers (94.5×41×37.5 cm). Each chamber had three compartments separated by two removable Plexiglas barriers. One compartment (40×41×37.5 cm) was black in color and had a smooth Plexiglas floor. Another compartment (40×41×37.5 cm) was white in color and had a natural wood grain floor with black sandpaper strips (2.54×41 cm) placed horizontally 2.54 cm apart. A third (central) compartment (11×41×37.5 cm) was gray in color and had a wire-mesh (23 gauge) floor. Each chamber was dimly lit with a 60-W Halogen bulb placed approximately 1.54 m overhead.

2.3. Drugs and solutions

Morphine sulfate (generously supplied by NIDA) was prepared as a 5 mg/ml solution in distilled water (drug vehicle). Saccharin (0.1% sodium saccharin, Sigma Chemical Co.) was prepared as a 1 g/l solution in tap water.

2.4. Procedure

2.4.1. Pre-conditioning

The rats were water deprived such that they received 20 min of water access daily for 1 week before commencement of conditioning.

2.4.2. Preexposure

Water consumption was recorded and averaged for each animal for the 3 days prior to the first preexposure day. So that each preexposure condition would be matched on fluid consumption, animals were assigned to one of two preexposure conditions, i.e., either morphine (M) or vehicle (V), based on this averaged water consumption. In this phase, all animals in Group M were given an injection of 5 mg/kg of morphine (sc) every other day for a total of five injections. Animals in Group V were given an injection of the drug's vehicle (distilled water), equivolume to the morphine dose (5 mg/kg), under the same preexposure injection schedule. Fluid consumption was measured on injection and non-injection days for the 10-day preexposure period.

2.4.3. Conditioning

Animals were run in six replicates of eight animals beginning at 0800 each morning. Each replicate was run one after another at the same time each day, and each contained at least one (maximum two) subject from each experimental group. On the first conditioning day (C1A), animals in each replicate were given 20-min access to a novel saccharin solution during their normal daily 20-min fluid-access period. Five min after the removal of the saccharin solution, the animals received an injection of either morphine (1 or 5 mg/kg) or equivolume (to the high dose; 5 mg/kg) drug vehicle (0 mg/kg) [thus generating 6 experimental conditions (M/0, M/1, M/5, V/0, V/1, V/5) defined by their preexposure group (M or V) and their conditioning dose (0, 1 or 5 mg/kg); n=8 per condition] after which they were placed in either the black or white compartment of the conditioned place preference (CPP) chamber for 30 min. Equal numbers of animals were placed in the black or white compartments, and their placement was randomly determined prior to commencement of the study using a counterbalanced design. On the next day (C1B), animals received 20-min access to water followed by an injection of the drug vehicle and then placed in the other of the black and white CPP compartments. These 2 days together (i.e., C1A and C1B) constituted one conditioning cycle, and each group went through four of these cycles.

2.4.4. CPP/CTA testing

On the day following each of the conditioning cycles (i.e., the day after C1B, C2B, C3B and C4B), all of the animals were given a test for CPP (see Gaiardi et al., 1991 for similar repeated testing of CPP after each conditioning cycle) where the animals were placed in the gray compartment and the two barriers separating the gray from the white and black compartments were removed. The animals were then given 20-min access to all of the compartments in a drug-free state. On the day following the final CPP test, all animals were given a final one-bottle aversion test in which they received 20-min access to the saccharin solution.

2.5. Data analysis

2.5.1. Preexposure

To assess any effect of non-contingent morphine exposure on fluid consumption during the preexposure period, water consumption was compared between the two preexposure groups (Groups M and V) on each of the preexposure days (1–10) using a 2×10 repeated measures analysis of variance (ANOVA).

2.5.2. Conditioning

Differences in saccharin consumption among the six groups were analyzed using a 2×3×5 univariate repeated measures ANOVA. The between factors were Preexposure Condition (morphine or vehicle) and Conditioning Dose (0, 1 or 5 mg/kg) and the within-factor was Trial (Trials 1–4 and the final aversion test). Place preferences were measured by comparing the average amount of time spent on the drug paired side (DPS) to the average amount of time spent on the non-drug paired side (NonDPS) within each of the experimental groups (Groups V/1, V/5, M/1 and M/5), at each trial, using Paired Sample *t*-tests. Differences among the groups in time spent on the drug paired side were analyzed using 2×2×4 repeated measures ANOVAs, with the between-group factors of Preexposure Condition (morphine or vehicle) and Conditioning Dose (1 or 5 mg/kg morphine) and the within-factor of Test (Tests 1–4). These repeated measures ANOVAs were followed by one-way ANOVAs for each Test and pair-wise comparisons, using Tukey HSD post hoc tests (Kramer correction). Alpha was set at 0.05.

3. Results

3.1. Conditioned taste aversion

3.1.1. Preexposure

During preexposure, the mean fluid consumption was assessed for the groups of animals preexposed to morphine and to distilled water over the 10-day preexposure period. The overall omnibus analysis revealed that there was no main effect of Preexposure Condition [$F(1,46)=0.133$, $p>0.05$] or significant Preexposure Condition × Day two-way interaction [$F(9,414)=1.373$, $p>0.05$]. These results suggest that there was no generalized suppressive effect of morphine on fluid consumption before the conditioning stage of the experiment commenced.

3.1.2. Conditioning

Fig. 1 illustrates saccharin consumption for all groups (i.e., Groups V/0, M/0, V/1, M/1, V/5, M/5) over each of the four conditioning trials and on the final aversion test. The omnibus 2×3×5 repeated measures ANOVA revealed significant between-group main effects of Preexposure Condition [$F(1,42)=28.641$, $p<0.001$] and Conditioning Dose [$F(2,42)=25.232$, $p<0.001$], as well as a significant within-group main effect of Trial [$F(4,168)=7.795$, $p<0.001$]. There were significant two-way interactions of Preexposure Condition × Trial [$F(4,168)= 21.891$, $p<0.001$] and Conditioning Dose × Trial [$F(8,168)= 17.665$, $p<0.001$]; however, the two-way interaction of Preexposure Condition × Conditioning Dose [$F(2,42)= 1.148$, $p=0.327$] was not significant. There was a significant three-way interaction of Preexposure Condition × Conditioning Dose × Trial [$F(8,168)=3.289$, $p<0.005$].

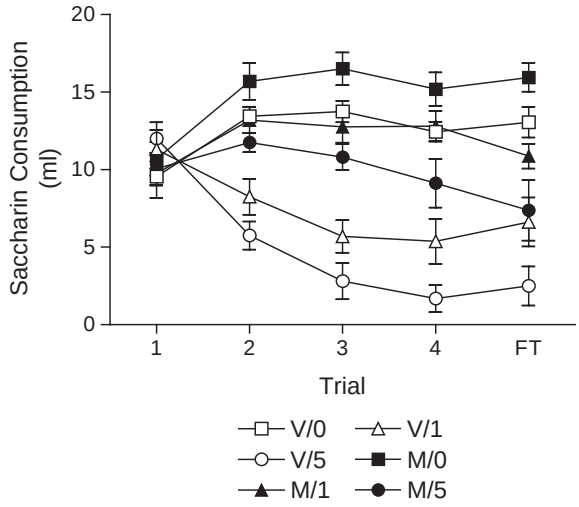

Fig. 1. Mean (±SEM) saccharin consumption (ml) for subjects preexposed to either morphine (M) or distilled water (V) and receiving saccharin-drug pairings (0, 1 or 5 mg/kg morphine) during taste aversion conditioning [Trial 1–4 and the final aversion test (FT)].

Given the significant two- and three-way interactions, one-way ANOVAs were performed at each of the four conditioning trials and on the final aversion test to examine differences among the groups at each of the time points. There were no significant differences in saccharin consumption among any of the groups on Trial 1 [($F(5,42)=0.735$, $p=0.601$]. There were significant group differences in saccharin consumption on each of the remaining conditioning trials and on the final aversion test, i.e., Trial 2 [$F(5,42)=16.09$, $p<0.001$], Trial 3 [$F(5,42)= 29.709$, $p<0.001$], Trial 4 [$F(5,42)=19.811$, $p<0.001$] and the final aversion test [$F(5,42)=13.605$, $p<0.001$]. To assess differences in saccharin consumption among specific groups at each trial, the above mentioned one-way ANOVAs were followed by post hoc pair-wise comparisons. As mentioned above, there were no significant differences in baseline saccharin consumption among groups on the initial conditioning trial. At no time during the remaining trials did saccharin consumption differ between the two control groups (i.e., Groups V/0 and M/0, $ps>0.05$) (see Fig. 1). After one conditioning trial (i.e., on Trial 2), the groups preexposed to the vehicle and conditioned with morphine (Groups V/1 and V/5) drank significantly less saccharin than subjects in Group V/0 ($ps<0.005$ and 0.001, respectively), although they did not

differ significantly from each other ($p>0.05$). Subjects preexposed to morphine and conditioned with the high dose of morphine (i.e., Group M/5) drank significantly less than Group M/0 ($p<0.05$). Each of the morphine preexposed, conditioned groups (i.e., Groups M/1 and M/5) drank significantly more saccharin than conditioned subjects injected with vehicle during preexposure (i.e., V/1<M/1, $p<0.01$; V/5<M/5, $p<0.001$). There were no other significant differences among groups on this trial.

On the remaining conditioning trials and on the final aversion test, vehicle-preexposed subjects conditioned with morphine (Groups V/1 and V/5) drank significantly less than controls (i.e., Groups V/0 and M/0; all $ps<0.05$), although these groups never differed from each other (all $ps>0.05$). Subjects preexposed and conditioned with the high dose of morphine (Group M/5) continued to drink significantly less than Group M/0 on all trials ($ps<0.01$) and from Group V/0 on the final aversion test ($p<0.05$), while Group M/1 did not differ from either control group. Both Groups M/1 and M/5 continued to drink significantly more than Groups V/1 and V/5, respectively (Groups M/1>V/1, $ps<0.005$; Groups M/5>V/5, $ps<0.001$) on Trials 3 and 4, but did not differ from these groups on the final aversion test. Neither Groups V/1 and V/5 nor Groups M/1 and M/5 differed at any point during conditioning or on the final aversion test.

3.2. Conditioned place preference

Figs. 2, 3 and 4 illustrate the amount of time spent on the DPS and the NonDPS for morphine and vehicle preexposed animals at each conditioning dose (Fig. 2: Groups V/0 and M/0; Fig. 3: Groups V/1 and M/1; Fig. 4: Groups V/5 and M/5) for each of these tests. For the control groups (i.e., Groups V/0 and M/0), the DPS was equivalent to the compartment in which animals were placed on the first day of each conditioning cycle (i.e., C1A, C2A, C3A, C4A) and NonDPS equivalent to the other of the two compartments. There were no significant differences between time spent on DPS and NonDPS for either control group at any of the tests [Tests 1–4, all $ts(7)<0.432$, $ps>0.05$]. Subjects preexposed to the vehicle and conditioned with the low dose of morphine (Group V/1) demonstrated a significant place

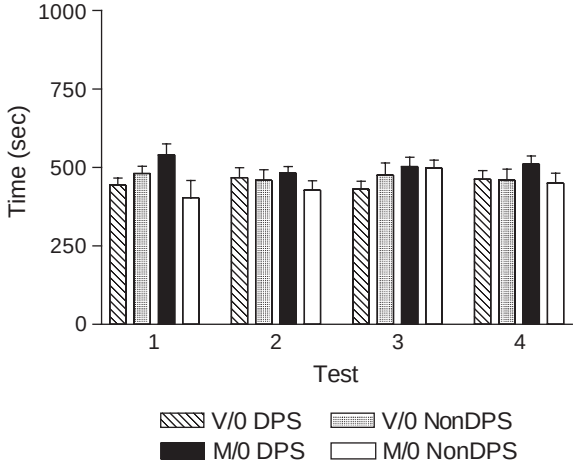

Fig. 2. Comparisons, after each conditioning trial, of the mean (±SEM) time (s) spent on the drug paired side (DPS) and the non-drug paired side (NonDPS) for those animals preexposed to either morphine (M) or distilled water (V) and conditioned with the drug vehicle (0 mg/kg). For these control animals the compartment in which they were placed on the first day of conditioning was designated their DPS, and the other compartment the NonDPS. There were no differences in time spent on the DPS and NonDPS for either of these groups at any test (i.e., Test 1–4).

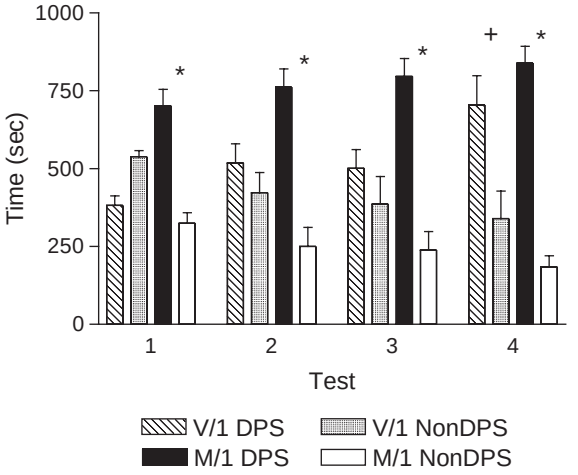

Fig. 3. Comparisons, after each conditioning trial, of the mean (±SEM) time (s) spent on the drug paired side (DPS) and the non-drug paired side (NonDPS) for those animals preexposed to either morphine (M) or distilled water (V) and conditioned with the lower dose (1 mg/kg) of morphine. (*) indicates a significant difference between the DPS and NonDPS for the morphine preexposed group (M/1) at the specific Test ($p<0.01$). (+) indicates a significant difference between the DPS and the NonDPS for the vehicle-preexposed group (V/1) at Test 4.

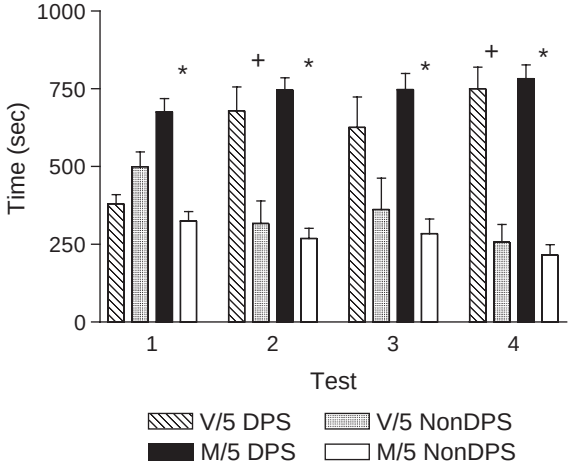

Fig. 4. Comparisons, after each conditioning trial, of the mean (±SEM) time (s) spent on the drug paired side (DPS) and the non-drug paired side (NonDPS) for those animals preexposed to either morphine (M) or distilled water (V) and conditioned with the higher dose (5 mg/kg) of morphine. (*) indicates a significant difference between the DPS and NonDPS for the morphine preexposed group (M/5) at the specific Test ($p<0.01$). (+) indicates a significant difference between the DPS and the NonDPS for the vehicle-preexposed group (V/5) at Tests 2 and 4.

preference (i.e., significantly greater amount of time spent on the DPS than the NonDPS) after the fourth conditioning trial [Test 4: $t(7)=3.434$, $p<0.01$]. There were no significant differences for this group on any other test [Tests 1–3, all ts(7)<0.799, ps>0.05]. Subjects preexposed to morphine and conditioned with the low dose of morphine (Group M/1) demonstrated a significant conditioned place preference on Test 1 [$t(7)=4.539$, $p<0.005$], Test 2 [$t(7)=4.366$, $p<0.005$], Test 3 [$t(7)=4.836$, $p<0.005$] and Test 4 [$t(7)=7.398$, $p<0.001$] (see Fig. 3). Animals preexposed to the vehicle and conditioned with the high dose of morphine (Group V/5) demonstrated a significant conditioned place preference on Test 2 [$t(7)=2.458$, $p<0.01$] and Test 4 [$t(7)=3.982$, $p<0.005$], but not on Tests 1 or 3 [ts(7)<1.36, ps>0.05]. Finally, animals preexposed to morphine and conditioned with the high dose of morphine (Group M/5) demonstrated a significant place preference on all tests, with significantly greater amount of time spent of DPS compared to NonDPS on Test 1 [$t(7)=4.943$, $p<0.005$], Test 2 [$t(7)=6.769$, $p<0.001$], Test 3 [$t(7)=4.864$, $p<0.005$] and Test 4 [$t(7)=7.964$, $p< 0.001$] (see Fig. 4).

A 2×2×4 repeated measures ANOVA on the amount of time spent on the DPS revealed significant main effects of Preexposure Condition [$F(1,28)=14.384$, $p<0.005$] and Test [$F(3,84)=23.735$, $p<0.001$] with no significant main effect of Conditioning Dose [$F(1,28)=0.212$, $p>0.05$]. There was a significant two-way interaction of Preexposure Condition × Test [$F(3,84)=5.689$, $p<0.005$]. There was no significant Conditioning Dose × Test [$F(3,84)=1.038$, $p>0.05$], Preexposure Condition × Conditioning Dose [$F(1,28)=1.432$, $p>0.05$] or Preexposure Condition × Conditioning Dose × Test interaction [$F(3,84)=0.828$, $p>0.05$].

To investigate the Preexposure × Test two-way interaction, independent-sample t-tests were performed for the two preexposure conditions (collapsed over Conditioning Dose) at each of the tests. Fig. 5 illustrates the amount of time spent on the DPS at each place preference test (i.e., Tests 1–4) for the morphine and vehicle preexposed groups (collapsed across Conditioning Dose, given that there was neither a significant main effect nor significant interaction with the factor of Dose). Animals that were preexposed to morphine spent significantly greater amounts of time on the DPS than did the vehicle-preexposed animals on Test 1 [$t(30)=7.947$, $p<0.001$], Test 2 [$t(30)=2.507$, $p<0.05$] and Test 3 [$t(30)=3.028$, $p<0.01$], but not on Test 4 [$t(30)=1.262$, $p>0.05$]. Given the overall omnibus, no other comparisons were warranted.

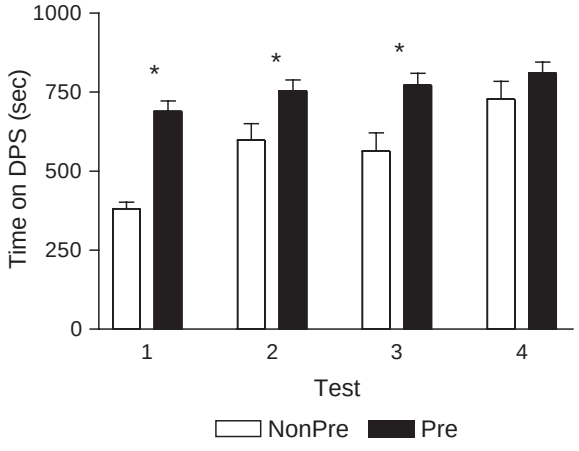

Fig. 5. Comparison of the mean (±SEM) time (s) spent on the drug paired side (DPS) between those animals with morphine preexposure (Pre) and those with vehicle preexposure (NonPre), collapsed across conditioning doses, after each conditioning trial (i.e., Tests 1–4). (*) indicates a significant difference at the specific Test ($p<0.05$).

4. Discussion

The fact that a history of morphine exposure differentially affects measures of drug reward and drug aversion (See Introduction) has led to different conclusions regarding the underlying mechanisms for enhanced CPPs (measure of drug reward) and attenuated CTAs (measure of drug aversion). Yet, actual empirical evidence for separate mechanisms is limited. For instance, Martin et al. (1988) argued for independent mechanisms given their findings within the same animals that morphine preexposure attenuated morphine-induced taste aversions without affecting the place preferences conditioned by morphine. However, their evaluation of enhanced place preferences was limited to a comparison of the degree of CPP between morphine preexposed and nonpreexposed animals tested at only one time point and conditioned with only one dose of morphine. Given that others have shown that morphine preexposure can increase the rate of acquisition of morphine-induced place preferences (Gaiardi et al., 1991; Shippenberg et al., 1996) and decrease the dose at which preferences can be conditioned (Lett, 1989), it is possible that sensitization did occur following drug preexposure that simply was not detected within the parameters used in its assessment. A more comprehensive assessment of morphine CPP including such measures may be necessary before drawing any conclusions regarding the independence of these underlying processes. Accordingly, the present study assessed the effects of five morphine preexposure injections at 5 mg/kg on morphine-induced CPP and CTA in the same animals conditioned with 0, 1 or 5 mg/kg of morphine and tested at multiple time points (after each conditioning cycle).

Consistent with independent reports demonstrating morphine-induced CTA or CPP under similar parameters (see Hunt and Amit, 1987 for review of CTA; see Riley and Freeman, 2004 for CTA bibliography; see Tzschentke, 1998 for review of CPP), as well as those concurrently assessing the opposite motivational properties of drugs (see Brockwell et al., 1991; Martin et al., 1988; Reicher and Holman, 1977; Sherman et al., 1980; Wise et al., 1976; though see Mayer and Parker, 1993), nonpreexposed animals in the present study demonstrated aversions to the saccharin that was

paired with a morphine injection and preferences for the place that was associated with the same drug. As described, animals that were preexposed to morphine drank significantly greater amounts of saccharin than those without such a drug history (Trials 2–4). These same animals demonstrated significantly enhanced place preferences, spending more time on the morphine-paired side of the CPP chamber and displaying significant preferences on earlier trials than animals with no drug preexposure. Thus, consistent with independent assessments of the effects of morphine preexposure on either CPP (e.g., Gaiardi et al., 1991; Lett, 1989; Shippenberg et al., 1996) or CTA (Stewart and Eikelboom, 1978; see Riley and Simpson, 2001, for review), chronic morphine preexposure both attenuated taste aversions and enhanced place preferences within the same animals and under identical parametric conditions.

As described above, Martin et al. (1988) reported clear attenuation of a morphine-induced conditioned taste aversion following morphine preexposure (relative to nonpreexposed subjects), yet no difference in the degree of morphine-induced place preferences between drug naïve and morphine preexposed subjects. The present experiment also found no difference in the degree of place preference observed at the high dose of morphine (5 mg/kg) between preexposed and nonpreexposed subjects tested after two conditioning trials. However, the fact that morphine preexposed animals demonstrated a significant place preference after only one conditioning trial, whereas those animals similarly conditioned but with no drug history showed no such preference, suggests a faster rate of acquisition of the CPP following morphine preexposure. Furthermore, morphine preexposed animals conditioned with the lower dose of morphine (1 mg/kg) demonstrated a CPP after fewer trials than similarly conditioned animals without preexposure, again suggesting enhanced place preferences following morphine preexposure.

The evidence of enhanced place preferences in the present study raises questions regarding the independence of the underlying mechanisms for enhanced CPP and CTA. Martin et al. (1988) argued that given the dissociation between these effects, they must be independent. The present findings, however, suggest that the attenuation of CTAs and the enhancement of CPPs follow very similar, almost identical, patterns of development, which is consistent with others who have made such assessments with morphine in separate groups of animals (see Gaiardi et al., 1991). Specifically, morphine preexposed subjects displayed attenuated taste aversions and enhanced place preferences after only a single conditioning trial and maintained these effects over the next two conditioning trials, i.e., on Tests 2 and 3. The effects of repeated exposure on aversions and preferences were no longer evident on the last test, i.e., on this test, drug naïve and morphine preexposed animals no longer differed in the display of either the CTA or the CPP. Such parallel findings might argue for a common mechanism occurring with morphine preexposure that manifests itself in both of these measures of morphine's motivational properties.

Although the effects of preexposure on aversion learning and place preferences were generally parallel over conditioning, there were instances where the parallel was not evident. For example, after two conditioning trials, morphine preexposure attenuated the taste aversion produced by the higher dose of morphine, whereas it did not sensitize the place preference produced by these same injections. The failure to see sensitization in the preexposed subjects at this point, however, may have been a function of a ceiling effect rather than the absence of sensitization. Although morphine is effective in conditioning place preferences over a broad dose-range (Mucha et al., 1982), the steep part of the dose–response curve for subcutaneously-administered morphine is between 0.04 and 1.0 mg/kg (Mucha and Iversen, 1984). This might suggest a greater sensitivity of the CPP design for changes in the rewarding properties of these lower doses of morphine and less discrimination of the rewarding impact of the higher doses (van der Kooy, 1987). The reduced sensitivity within this design at higher doses of morphine may act like a ceiling, obscuring any increased effects of chronic morphine exposure. If this ceiling was reached in a single trial for the morphine preexposed subjects and after two trials in the vehicle-treated animals, then further conditioning would not reveal any greater place preference and, thus, the differences between the two groups would be masked. Assessing the effects of drug preexposure on place preferences with lower conditioning doses might provide a direct test of this possibility of the apparent dissociation.

Although the data presented in this study suggest a common underlying mechanism, the nature of this mechanism remains unclear, as these findings can be interpreted in multiple ways and are consistent with more than one mechanism. For instance, Gaiardi et al. (1991) argued that the attenuation of morphine-induced taste aversions observed after morphine preexposure was due to reward sensitization given the sensitized morphine-induced place preferences observed after a similar preexposure regimen administered to another group of animals. That is, increases in the rewarding properties resulting from drug preexposure may decrease the overall perceived aversive value of morphine that would be manifested in a weaker taste aversion. The present findings are certainly consistent with this conclusion; however, they are also consistent with other mechanisms which argue that a decrease in the aversive effects during drug preexposure mediates increased place preferences (see Riley and Simpson, 2001). That is, decreases in the aversive properties that result from drug preexposure (e.g., drug tolerance; Goldstein et al., 1974) may increase the overall perceived rewarding value of morphine that would subsequently be manifested in the observed enhanced place preferences.

Each of the two aforementioned explanations assumes that there is a common mechanism, i.e., either sensitization to the rewarding effects or a weakening of the aversive

effects, underlying the two effects of drug preexposure, i.e., increased conditioned place preferences and attenuated taste aversions. However, the possibility exists that different mechanisms are occurring concurrently and are responsible for the attenuation of taste aversions and for the enhancement of place preferences after drug preexposure. Evidence suggesting dissociation of the attenuation of taste aversions and the sensitization of place preferences might provide support for separate mechanisms underlying the effects seen with drug preexposure.

Although direct tests of this possibility are limited, several have been made. For example, in an examination of the context-specificity of UCS preexposure on place conditioning with morphine, McKee et al. (1994) reported that under identical preexposure parameters (in different groups of animals) morphine-induced CTAs were attenuated in animals that received morphine preexposure, whereas the morphine-induced CPPs were unaffected. Similarly, Cunningham et al. (2002) have reported that under identical parametric conditions repeated ethanol exposure in mice attenuated a measure of drug aversion (place aversion), with no impact on a measure of drug reward (place preference). It was argued that given the differential impact on these assessments, drug preexposure must have affected ethanol's aversive properties, but not ethanol's rewarding properties. In a similar examination of the effects of ethanol preexposure on both place preferences and taste aversions, Davies and Parker (1990) demonstrated that ethanol preexposure attenuated ethanol-induced CTAs but had no effect on a measure of ethanol-induced CPP. It should be noted, however, that although consistent with a dissociation of the impact of ethanol preexposure on these two behavioral measures, there was no evidence of ethanol-induced CPP, regardless of preexposure condition, limiting conclusions regarding the lack of change in CPP after ethanol preexposure. It is not clear to what extent the findings of these studies might generalize to other recreational compounds, but it is clear that the attenuating effects of drug exposure on aversion learning can be independent of any changes in the rewarding effects of the drug.

The present investigation has explored the effects of morphine preexposure on measures of drug reward and drug aversion. In doing so, consideration has been given to the relative changes in the rewarding and aversive effects following morphine exposure, changes that may have implications for drug use and abuse. The interaction of these motivational properties (i.e., rewarding and aversive properties) of drugs of abuse has been suggested to have an influence on drug acceptability (Grakalic and Riley, 2002; Riley and Simpson, 2001) and drug seeking behavior (Goudie, 1979; Stolerman, 1992). Consequently, information regarding the relative contribution of these factors (and how they might change with drug history) may give insight into their respective role in such behavior. The present study has demonstrated that drug history results in a change in the ability of morphine to induce an aversion while at the same time demonstrating that the same drug is more likely to induce a place preference. Independent of whether these changes in conditioning reflect a decrease in the aversive effects of morphine, an increase in the rewarding effects of morphine or changes in both processes, the affective properties of morphine were impacted and in a direction that is likely to be associated with increased drug intake. By assessing the effects of various preexposure manipulations on the concurrent acquisition of CTAs and CPPs, the basis for these changes may become evident. Determining the specific mechanism underlying changes in the affective properties of drugs with such exposure may give insight into techniques and strategies for altering these properties to help in abuse prevention and treatment.

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