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Effects of β-funaltrexamine and naloxonazine on single-trial morphine-conditioned place preference and locomotor activity

M.T. Bardo*, B.J. Gehrke, B.E. Shortridge, A.S. Rauhut

Department of Psychology, University of Kentucky, Lexington, KY 40506-0044, USA

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Abstract

The current study assessed the ability of the selective irreversible μ-opioid receptor antagonists β-funaltrexamine (βFNA) and naloxonazine (NALZ) to alter the locomotor and rewarding effects of a single intravenous injection of morphine using the conditioned place preference (CPP) model. In the first experiment, rats were conditioned with a single injection of morphine (10 mg/kg iv) paired with one compartment of a CPP apparatus and then were tested for CPP at either 1 or 7 days after conditioning. Rats showed hypoactivity following acute morphine on the conditioning trial and showed CPP when tested either 1 or 7 days later. In the next experiments, rats were pretreated with βFNA (20 mg/kg sc, 20 h before conditioning), NALZ (15 or 30 mg/kg sc, 24 h before conditioning) or saline and then were conditioned with a single injection of morphine (10 mg/kg iv) or saline. Pretreatment with NALZ alone, but not βFNA, significantly decreased locomotor activity; neither antagonist alone produced a significant shift in preference for either compartment of the CPP apparatus. Pretreatment with either βFNA or NALZ blocked completely morphine-induced hypoactivity, but neither antagonist had a significant effect on morphine CPP. These results indicate that μ-opioid receptors are more critically involved in acute morphine-induced hypoactivity than in acute morphine reward.

Keywords: μ-Opioid receptors; Morphine; β-funaltrexamine; Naloxonazine; Conditioned place preference; Locomotor activity; Opiate reward

1. Introduction

Considerable research has been aimed at uncovering the basic neuropharmacological mechanisms that mediate opiate reward. Recent reviews of the extensive literature indicate that multiple neuroanatomical systems are involved, including the ventral tegmental area, nucleus accumbens, lateral hypothalamus, hippocampus, and amygdala (Bardo, 1998; Shippenberg and Elmer, 1998). Various neural circuits have been implicated by using either the opiate intravenous self-administration or conditioned place preference (CPP) models. While use of these two models of opiate reward have tended to yield similar conclusions, it appears that the mesolimbic dopamine system is more critically involved in opiate CPP than opiate self-administration (Shippenberg and Elmer, 1998).

One potential limitation in examining the mechanisms of opiate reward using either intravenous self-administration or CPP is that these models utilize repeated drug exposure regimens. In the case of self-administration, multiple self-infusions over repeated sessions are examined; in the case of CPP, four drug conditioning trials are typically used (Bardo et al., 1995). Since repeated exposure to drugs of abuse may induce sensitization, tolerance, and/or physical dependence in the self-administration and CPP models (Catarino et al., 1997; Lett, 1989; Schenk and Partridge, 1997; Shippenberg et al., 1996), it may not be possible to determine if a treatment that alters opiate self-administration or CPP is working on the mechanism involved in the acute rewarding effect of opiates or the mechanisms involved in sensitization, tolerance, and/or physical dependence.

The single-trial CPP procedure has been developed as a model to examine the acute rewarding effect of opiates. Single-trial CPP has been demonstrated using a single intravenous injection of morphine (Mucha et al., 1982). Opioid receptors are known to be involved in this effect, as pretreatment with naloxone reverses single-trial morphine CPP (Bardo and Neisewander, 1986). However, since

* Corresponding author. Tel.: +1-859-257-6456; fax: +1-859-323-1979.
E-mail address: mbardo@uky.edu (M.T. Bardo).

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naloxone is a relatively nonselective opioid antagonist that does not differentiate among the various opioid receptor subtypes, the specific role of μ-, δ- and κ-subtypes in single-trial morphine CPP is unknown.

The purpose of the present study was twofold. First, the present study investigated whether single-trial morphine CPP is a transient or long-lasting phenomenon. This question was addressed by testing separate groups of rats for CPP at 1 or 7 days after conditioning (Experiment 1). Second, the present study examined whether μ-opioid receptors are specifically involved in the development of single-trial morphine CPP (Experiments 2 and 3). The role of μ-opioid receptors in the locomotor effect of acute intravenous morphine was also examined.

2. Methods

2.1. Animals

Adult male Sprague–Dawley rats (200–300 g body weight) obtained from Harlan Industries (Indianapolis, IN) were used. Rats were maintained individually in standard polypropylene cages, with pine chip bedding and wire mesh top, in a colony room in which the lights came on at 0600 h and went off at 2000 h; all experimental procedures were conducted during the light phase. Food and water were available continuously in the home cage. Upon arrival, the rats were acclimated to the colony for at least 5 days and were handled briefly prior to the start of the experiment. The experiments were approved by the Institutional Animal Care and Use Committee at the University of Kentucky, and the procedures conformed to the guidelines established by the *NIH Guide for the Care and Use of Laboratory Animals* (1996 Edition).

2.2. Apparatus

For assessment of locomotor activity and CPP, a wooden apparatus was used that had three different compartments separated by removable partitions. The two end compartments measured $24 \times 30 \times 45$ cm high, while the middle compartment was smaller and measured $24 \times 10 \times 45$ cm high. One end compartment had white walls, a wire mesh floor, and pine bedding beneath the floor. The other end compartment had black walls, a metal rod floor, and either cedar chips (Experiments 1 and 2) or pine chips (Experiment 3) beneath the floor; the bedding was changed for Experiment 3 in order to reduce the baseline preference for the white compartment (see later results). The middle compartment had gray walls and a solid wood floor. The solid partitions could be replaced with similar partitions containing a 10×10-cm opening, which allowed the animals access to all compartments. The apparatus was located in a laboratory room that was separate from the colony room and was equipped with a white noise generator and audio speaker (ambient background of 70 dB). Suspended from the ceiling above the apparatus was a video camera which was used to record the experimental sessions.

2.3. Drugs

Morphine sulfate (National Institute on Drug Abuse, Bethesda, MD) was mixed in a 0.9% NaCl solution and injected subcutaneously (sc). The volume of each injection was 1 ml/kg body weight. The selective irreversible μ-opioid receptor antagonists, β-funaltrexamine (βFNA) hydrochloride (Research Triangle Institute, Durham, NC) and naloxonazine (NALZ) dihydrochloride (RBI/Sigma, St. Louis, MO), were dissolved in 0.9% NaCl and injected sc at a volume of either 5 ml/kg (NALZ) or 10 ml/kg (βFNA) body weight. Doses are expressed based on salt weights.

2.4. Procedure

2.4.1. Experiment 1

Rats ($n = 26$) were anesthetized (80 mg/kg ketamine and 5 mg/kg diazepam ip) and implanted with a chronic indwelling catheter into the jugular vein. The end of the catheter exited from the mid-scapular region of the back. Attached to end of the catheter was a 1.5-cm piece of metal tubing, capped with a plastic end joint, that served as a connector for drug injection. Daily flushes of heparinized saline were used to maintain catheter patency.

Following 3–4 days of recovery from the surgery, rats were assigned to a 2×2 (drug × test delay) factorial design in which each rat was conditioned with either morphine or saline and was tested for CPP following either a 1- or 7-day delay. A pretest session was first conducted 1 day prior to the start of conditioning. During the pretest, animals were placed into the center compartment of the CPP apparatus and were allowed to explore all three compartments for 15 min. The conditioning procedure was then conducted over two consecutive days. On day 1, animals were placed individually into either the white or black end compartment for 30 min with solid partitions inserted between the compartments. On day 2, animals were placed into the opposite compartment for 30 min. Conditioned animals were injected with morphine (10 mg/kg iv) immediately following placement into either the white or black compartment (counterbalanced) and were injected with saline immediately following placement into the opposite compartment. Control animals received saline in both compartments. At either 1 or 7 days after conditioning, each rat was placed into the center compartment and allowed free access to all compartments for 15 min.

To assess activity during conditioning, videotapes were scored for both horizontal and vertical activity by an observer who was unaware of the treatment condition for each individual rat. Horizontal activity was quantified by counting the number of times that both front paws of the rat crossed over a line that bisected each compartment on the

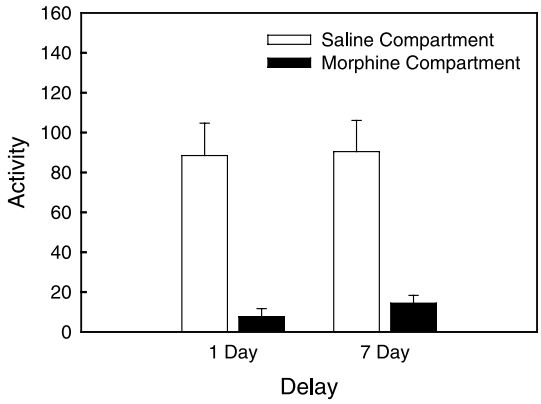

Fig. 1. Activity in the morphine- and saline-paired compartments during the conditioning trial in rats subsequently tested for CPP either 1 or 7 days after conditioning in Experiment 1. Activity was defined as the mean (+S.E.M.) number of line crosses and rears (combined). The ANOVA revealed a significant main effect of morphine, $P<.05$.

video screen. Vertical activity was quantified by counting the number of times that the rat reared with both front paws off of the floor, excluding bouts of grooming. Statistical analyses were performed on total activity scores, defined as the combined number of line crosses and rears observed across the 30-min conditioning trial.

To assess CPP, the time spent in the white and black compartments on both the preconditioning and postconditioning tests was measured by an observer who was unaware of the treatment condition for each individual rat. For morphine-conditioned groups, the CPP data were expressed as a preference ratio. The preference ratio on the preconditioning test and postconditioning test was calculated as the time spent in the morphine-paired compartment divided by the time spent in both the white and black compartments. Morphine CPP was defined as a significant increase in the preference ratio from the preconditioning to the postconditioning test.

2.4.2. Experiments 2 and 3

In Experiment 2, rats ($n=30$) were assigned randomly to a 2×2 (βFNA × morphine) factorial design. Animals received the same surgical and single-trial conditioning procedures described in Experiment 1. However, each animal was pretreated with either βFNA (20 mg/kg sc) or saline in the colony room 20 h prior to the conditioning session with morphine (10 mg/kg iv); no pretreatment injection was given prior to the conditioning session with saline. The 20-h pretreatment interval was chosen in order to avoid the transient κ-agonist activity evident following acute βFNA (Ward et al., 1982). Saline controls also received either βFNA or saline pretreatment 20 h prior to placement into one of the compartments (counterbalanced). The rats were tested for CPP 7 days following the last day of conditioning.

In Experiment 3, rats ($n=48$) were assigned randomly to a 3×2 (NALZ × morphine) factorial design. The procedures were similar to Experiment 2, except the pretreatment was NALZ (0, 15, or 30 mg/kg sc) and the interval between pretreatment and conditioning was 24 h. As noted previously, the black compartment also had pine chip bedding, rather than cedar bedding beneath the floor.

2.5. Data analysis

Activity scores and preference ratios were analyzed using analyses of variance (ANOVA). Tukey's HSD tests were used for post hoc comparisons between groups, with statistical significance declared at $P<.05$.

3. Results

3.1. Experiment 1

During conditioning, the activity scores in the saline control groups (1- and 7-day delays) did not differ between the white and black compartments; mean (±S.E.M.) number of activity counts in the white compartment was 86±12 and in the black compartment was 93±10. In contrast, the morphine-conditioned group showed a significant decrease in activity on the conditioning trial in the morphine-paired compartment compared to the saline-paired compartment [$F(1,22)=45.33$, $P<.001$] (Fig. 1). There was no significant interaction between the compartment (morphine-paired vs. saline-paired) and delay (1-day vs. 7-day) factors in the ANOVA.

For the CPP data, there was a significant main effect of conditioning compartment for the saline control group [$F(1,11)=21.21$, $P<.001$] with animals showing an overall significant preference for the white compartment compared to the black compartment (Table 1). No significant shift in preference from the preconditioning to postconditioning test in the saline control group was obtained (Table 1), although there was an overall decrease in the total duration spent in both compartments on the postconditioning test. This latter effect was likely due to increased exploration of the center gray compartment, as it was relatively more novel than the end compartments following conditioning (see Bardo et al., 1995). More important, morphine-conditioned rats showed a significant increase in the preference ratio from the preconditioning to postconditioning test [$F(1,11)=22.29$, $P<.001$] indicating that

Table 1
Mean seconds (±S.E.M.) spent in the white and black compartments by saline control groups in Experiments 1–3

	Preconditioning		Postconditioning	
	White	Black	White	Black
Experiment 1	345±23	248±30	270±26	138±13
Experiment 2	328±17	258±14	262±14	215±18
Experiment 3	274±23	343±15	215±17	311±20

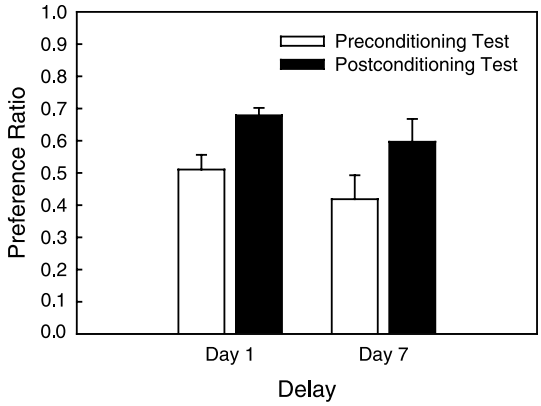

Fig. 2. Preference ratios on the preconditioning and postconditioning tests in rats conditioned with morphine and tested either 1 or 7 days after conditioning in Experiment 1. Preference ratio was defined as the mean (+S.E.M.) time spent in the morphine-paired compartment divided by the time spent in both the white and black compartments. The ANOVA revealed a significant main effect of test, with morphine producing an increase in the postconditioning preference ratio, $P<.05$.

morphine CPP was obtained at both test delay intervals (Fig. 2). In morphine-conditioned animals, there was no significant interaction between the test (preconditioning vs. postconditioning) and delay (1-day vs. 7-day) factors in the ANOVA [$F(1,11)=0.89$, $P>.05$].

3.2. Experiments 2 and 3

During conditioning, activity for the saline control groups in Experiments 2 and 3 did not differ significantly between the white and black compartments. ANOVA of the activity results revealed a significant interaction between the βFNA and morphine factors in Experiment 2 [$F(1,26)=8.76$, $P<.01$] and a significant interaction between NALZ and morphine factors in Experiment 3 [$F(2,42)=17.20$, $P<.001$]. Subsequent post hoc tests within each experiment revealed that 20 mg/kg βFNA pretreatment alone did not significantly alter activity compared to the saline control, whereas 30 mg/kg NALZ significantly decreased activity compared to the saline control (Fig. 3, cf., SAL+SAL vs. NALZ+SAL groups). More important, as summarized in Fig. 3, morphine significantly reduced activity in saline-pretreated rats, but not in rats pretreated with either βFNA (20 mg/kg) or NALZ (30 mg/kg), indicating that morphine-induced hypoactivity was blocked by both antagonists. The lower dose of NALZ (15 mg/kg) also blocked morphine-induced hypoactivity; mean (±S.E.M.) activity scores for these NALZ+SAL and NALZ+MOR groups were 79.8±10.6 and 96.1±20.4, respectively.

Analysis of the CPP data revealed no significant difference in the duration spent in the white and black compartments during either the preconditioning or postconditioning preference tests in the saline control groups from Experiments 2 and 3 (Table 1). Further, there was no significant change in preference ratio from the preconditioning to postconditioning test in the saline control groups, although there was an overall decrease in the total duration spent in both compartments on the postconditioning test (Table 1). When given alone, neither antagonist produced a significant alteration in preference; the mean (±S.E.M.) preconditioning and postconditioning preference ratios for the group given 20 mg/kg βFNA alone were 0.47±0.07 and 0.50±0.06, for the group given 15 mg/kg NALZ alone were 0.50±0.04 and 0.55±0.04, and for the group given 30 mg/kg NALZ alone were 0.53±0.02 and 0.52±0.04. More important, the overall ANOVA from the morphine-conditioned groups revealed that there was a significant main effect of test in Experiment 2 [$F(1,14)=10.69$, $P<.01$] and in Experiment 3 [$F(1,21)=5.08$, $P<.05$]. As shown in Fig. 4, regardless whether rats were pretreated with 20 mg/kg βFNA, 30 mg/kg NALZ, or saline, the preference ratio increased from the preconditioning test to the postconditioning test, an effect indicative of morphine CPP. The mean (±S.E.M.) preconditioning and postconditioning preference ratios for the group given the lower dose of NALZ (15 mg/kg) and morphine were 0.51±0.04 and 0.53±0.07. There was no

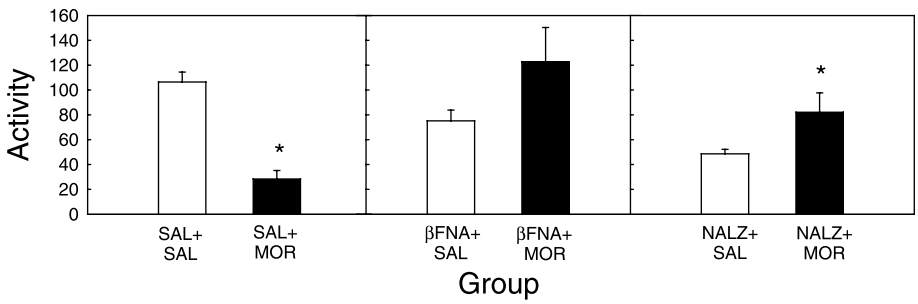

Fig. 3. Activity during the conditioning trial from rats pretreated with saline, βFNA (20 mg/kg) or NALZ (30 mg/kg) and then injected with either saline or morphine in Experiments 2 and 3. Activity was defined as the mean (+S.E.M.) number of line crosses and rears (combined). For the purpose of graphical presentation, the saline-pretreated groups are collapsed across Experiments 2 and 3 in the left panel and only the high dose of NALZ (30 mg/kg) is presented in the right panel. Asterisk (*) represents a significant difference from the SAL+SAL group, $P<.05$.

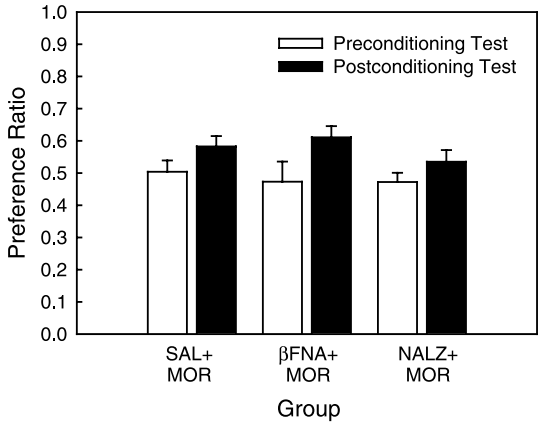

Fig. 4. Preference ratios on the preconditioning and postconditioning tests in rats pretreated with saline, βFNA (20 mg/kg) or NALZ (30 mg/kg) and conditioned with morphine in Experiments 2 and 3. Preference ratio was defined as the mean (+S.E.M.) time spent in the morphine-paired compartment divided by the time spent in both the white and black compartments. For the purpose of graphical presentation, the saline pretreated groups are collapsed across Experiments 2 and 3 in the left bars and only the high dose of NALZ (30 mg/kg) is presented in the right bars. The ANOVA from each experiment revealed a significant main effect of test, with morphine producing an increase in the postconditioning preference ratio regardless of antagonist pretreatment, $P<.05$ in each case.

significant interaction between the test and antagonist factors in either Experiment 2 [$F(1,26)=0.65$, $P>.05$] or Experiment 3 [$F(2,21)=0.45$, $P>.05$] indicating that neither antagonist reliably altered morphine CPP.

4. Discussion

Previous work has shown that CPP is obtained in a single trial using intravenous morphine (Bardo and Neisewander, 1986; Mucha et al., 1982). In that work, single-trial morphine CPP was assessed 1 day after conditioning. The current results extend this previous work by showing that single-trial morphine CPP is maintained even when the test session is delayed for 7 days. It is notable that multiple-trial morphine CPP can be extinguished within 3 days if rats are given repeated preference test days in the absence of drug (Parker and McDonald, 2000). In addition, single-trial morphine CPP can be extinguished if the effect of morphine is reversed by naloxone half-way through the conditioning trial (Bardo and Neisewander, 1986). Thus, these results support the notion that single-trial morphine CPP represents a Pavlovian conditioned response that does not decay merely with the passage of time, but that exposure to the CS alone after conditioning is required in order to extinguish the response.

Previous work has shown that single-trial morphine CPP is blocked by naloxone administered during the conditioning trial (Bardo and Neisewander, 1986). This effect is not unique to single-trial morphine CPP, as multiple-trial CPP using intravenous morphine is also reversed by naloxone (Mucha et al., 1982). In contrast, the present results found that single-trial morphine CPP was not blocked by either βFNA or NALZ. Since naloxone is a relatively nonselective opioid antagonist, whereas βFNA and NALZ have selectivity for the μ-opioid subtype (Pasternak, 2001; Ward et al., 1982), these results collectively suggest that morphine CPP is mediated, at least in part, by non-μ-type receptors. These opioid receptors most likely include the δ-subtype, since δ-agonists are known to produce CPP (Shippenberg et al., 1987). Importantly, doses of βFNA (20 mg/kg) and NALZ (15 or 30 mg/kg) used in the present study were found to reverse completely the morphine-induced decrease in locomotor activity. Taken together, it appears that μ-opioid receptors are more critically involved in the acute expression of morphine-induced hypoactivity than in expression of morphine CPP.

The present results appear to be at odds with recent data implicating a critical role for μ-opioid receptors in morphine reward using either the self-administration or CPP models. With self-administration, selective μ-agonists are known to be readily self-administered (Zernig et al., 1997) and the reinforcing effect of heroin is decreased by βFNA (Negus et al., 1993). In addition, mice lacking μ-opioid receptors fail to display reliable morphine self-administration behavior (Becker et al., 2000). With CPP, NALZ blocks morphine CPP (Piepponen et al., 1997) and mice lacking μ-opioid receptors fail to display morphine CPP (Matthes et al., 1996). While this clearly implicates a critical role for μ-receptors in opiate reward, it is important to note that these previous studies used a repeated dosing regimen, which may engender self-administration and CPP behavior due to, at least in part, the induction of sensitization and/or physical dependence. In contrast, the current study used a single-dose procedure which obviated this possibility. Perhaps the μ-opioid receptor plays a more prominent role in establishing morphine reward across repeated injections, rather than on the first injection.

Finally, it is possible that the failure to reverse single-trial morphine CPP may have been due to an incomplete blockade of μ-opioid receptors by the βFNA or NALZ pretreatments. That is, perhaps some μ-receptors were available for occupation by morphine on the conditioning day and these spared receptors were sufficient for establishment of morphine CPP. In support of this possibility, previous work has shown that βFNA alkylates only about 50% of available μ-opioid receptors (Franklin and Traynor, 1991) and that the full reinforcing effect of heroin can be obtained in the self-administration paradigm even when βFNA blocks a substantial portion of μ-binding sites (Martin et al., 1998). However, since the βFNA and NALZ pretreatments were sufficient to reverse completely morphine-induced hypoactivity in the present report, this suggests that fewer μ-opioid receptors may be needed to produce acute morphine reward than to produce acute morphine-induced hypoactivity. Furthermore, evidence indicates that there may functional cooperativity between μ- and δ-type

opioid receptors such that full expression of δ-mediated behaviors requires some minimal activation of μ-opioid receptors (Jiang et al., 1990; Matthes et al., 1998). This leaves open the possibility that the single-trial morphine CPP obtained here reflects a δ-mediated effect that was enabled due to some minimal activation of μ-receptors.

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