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Sensitization to the conditioned rewarding effects of morphine: pharmacology and temporal characteristics

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Abstract

An unbiased place preference conditioning procedure was used to determine whether the repeated administration of morphine results in sensitization to its conditioned rewarding effects. Rats received once daily injections of saline or morphine (5.0 mg/kg; i.p.) for 5 days in a room distinct from that where conditioning would occur. Place preference conditioning commenced 72 h later. A minimum of three drug conditioning sessions was necessary for the establishment of morphine-induced conditioned place preferences in saline-pretreated rats. The minimum dose producing this effect was 5.0 mg/kg. In animals pre-exposed to morphine, significant place preferences occurred after only two drug conditioning sessions and in response to doses of 3.0 mg/kg and greater. The augmented response to morphine was apparent when conditioning commenced 3, 10 or 21 days after the cessation of morphine pretreatment. It was not apparent when conditioning commenced 1 day after treatment cessation. An enhanced response to morphine was also observed in rats which had previously received either fentanyl (0.016 mg/kg/day) or nicotine (0.4 mg/kg/day) for 5 days. Animals which received morphine or fentanyl in combination with naloxone (0.5 mg/kg; s.c.) for 5 days failed to exhibit a conditioned response to morphine. When, however, naloxone was administered in combination with nicotine, significant morphine-induced place preferences were still seen. These data demonstrate that both sensitization and cross-sensitization develop to the conditioned rewarding effects of morphine. Furthermore, they indicate that the sensitization induced by morphine and fentanyl, but not nicotine, is opioid-receptor mediated.

Keywords: Sensitization; Morphine; Opioid; Psychostimulant; Conditioned reward; Place preference conditioning

1. Introduction

In recent years, it has become apparent that the repeated administration of psychostimulants as well as opioids can result in an enhancement of their behavioral effects (Babbini et al., 1975; Kalivas and Stewart, 1991; Stewart and Badiani, 1993). This phenomenon, referred to as sensitization, is thought to play an important role in the psychopathology of drug abuse as well as in the reinstatement of compulsive drug-seeking behavior which occurs in former drug addicts following periods of abstinence (Robinson and Berrige, 1993; Stewart and Eikelborn, 1987; Stewart and Badiani, 1993).

Several studies (Horger et al., 1990; Piazza et al., 1990; Valdez and Schenk, 1994) have shown that the repeated administration of psychostimulants can result in sensitization to their positive rewarding effects. The rate of acquisition of cocaine and amphetamine self-administration is accelerated in animals which previously received daily injections of cocaine or amphetamine. Furthermore, the number of animals exhibiting stable self-administration behavior is increased. Evidence that the conditioned rewarding effects of cocaine is enhanced in animals with a prior history of psychostimulant administration has also been presented (Lett, 1989; Shippenberg and Heidbreder, 1995).

Fundamental questions remain as to whether sensitization develops to the rewarding effects of opioids. Although evidence of an enhancement of the conditioned rewarding effects of morphine in animals with a prior history of opioid administration has been presented (Gaiardi et al., 1991; Lett, 1989), such findings have not been universal. Thus, tolerance (Shippenberg et al., 1988) or no alteration (Martin et al., 1988) in the conditioned rewarding effects of morphine have also been reported. At present, an explanation for these disparate results is lacking. It is, however, interesting to note that in these latter studies, place conditioning commenced within 1 day after the cessation of opioid exposure. In those studies, however, where an

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enhanced response to morphine has been observed, a period of drug abstinence preceded the commencement of place conditioning. Such findings suggest that the interval between drug exposure and subsequent testing may be an important factor in determining whether sensitization develops to the conditioned rewarding of opioids.

Accordingly, the present place conditioning studies sought to characterize the conditioned rewarding effect of morphine in animals with a prior history of opioid exposure as a function of both the dose of morphine administered and the time elapsed between drug pre-exposure and subsequent place conditioning. The issue of whether the repeated administration of other drugs of abuse can also result in an enhancement of the conditioned rewarding effects of morphine was also examined.

2. Materials and methods

2.1. Subjects

Male Sprague-Dawley rats (Charles River, Wilmington, MA, USA), weighing 225–275 g, were housed four per cage in a temperature-controlled colony room. They were maintained on a 12 h:12 h light:dark cycle (lights on: 07:00 h) with food and water available ad libitum. They were housed in the colony for at least 1 week prior to commencement of experiments. The colony was maintained in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care and all experiments were conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Addiction Research Center/NIDA/NIH.

2.2. Apparatus

Place conditioning was conducted in $30 \times 60 \times 30$ cm wooden shuttleboxes. Each was equipped with a lid and clear Plexiglas front. For conditioning sessions, the boxes were divided into two equal-sized compartments by means of a removable partition. One compartment was white and had a white textured Plexiglas floor. The other was black with a smooth black floor. For test sessions, the partition was raised 12 cm above the floor and a 5×2 cm 'neutral' steel mesh platform was inserted along the seam separating the two compartments. All sessions were conducted under conditions of dim illumination (8.5–9.5 lux) with masking white noise present. Previous studies (Shippenberg and Heidbreder, 1995) revealed that under these conditions, Sprague-Dawley rats exhibit no preference for either of the place cues.

2.3. Place conditioning

Place conditioning was conducted using an unbiased procedure (Shippenberg and Heidbreder, 1995). Sessions were conducted twice each day with 6–8 h separating each. Prior to each session, rats were wheeled into the room housing the shuttleboxes and allowed to habituate to this environment for 15 min. They were then injected with saline and immediately confined to one compartment of the shuttlebox for 50 min. Following administration of morphine, they were confined to the other compartment for 50 min. Treatment compartment and the presentation order of morphine and saline were counterbalanced for each drug dose. Tests of conditioning were conducted 1 day after the last conditioning session and each animal was tested only once. For test sessions, uninjected rats were allowed free access to both compartments of the shuttlebox for 15 min. The time spent in the morphine- and saline-paired environments was then assessed by visual analysis of the video-recorded test session. The location of the animal was determined by the position of the front paws. Analysis of the videotapes was conducted by an observer blinded to the experimental conditions.

2.4. Drugs

Naloxone hydrochloride (Sigma Chemical, St. Louis, MO, USA), morphine sulfate and fentanyl citrate (NIDA Drug Supply, Rockville, MD, USA) were dissolved in saline and administered s.c. Nicotine tartrate (Sigma Chemical Co., St. Louis, MO, USA) was administered i.p. The volume of all injections was 1.0 ml/kg. All doses refer to the base weight.

2.5. Characterization of morphine-induced place conditioning in opioid-naive rats

In initial experiments, the dose-effect curve for morphine and the number of conditioning sessions necessary for the establishment of place conditioning was determined in opioid-naive subjects. All animals received once daily injections of saline for 5 days in the colony room. Three days later, they were randomly assigned to one of ten groups (6–10 rats/group) for place conditioning. Separate groups of rats were then conditioned with either saline, 1.0, 3.0 or 5.0 mg/kg morphine. Either two or three drug conditioning sessions were conducted. Since these results indicated that morphine was ineffective as a conditioning stimulus after two drug conditioning sessions, a total of two drug sessions was used for all subsequent experiments.

2.6. Influence of prior morphine administration upon morphine-induced place conditioning

Animals (8–10/group) received s.c. injections of morphine (5.0 mg/kg) once daily for 5 days (days 1–5) in the colony room. Place conditioning commenced 3 days after the termination of injections and was conducted on days 8–9. On each of these days, animals received one condi-

tioning session with morphine (1.0, 3.0 or 5.0 mg/kg) and one with saline. Tests of conditioning occurred on day 10.

2.7. Morphine-induced conditioning as a function of the interval between drug pre-exposure and onset of place conditioning

Animals received once daily injections of morphine (5.0 mg/kg) for 5 days. Conditioning sessions (morphine 5.0 mg/kg vs. saline) commenced 1–21 days after the cessation of injections. For each time point evaluated, 6–8 rats were employed.

2.8. Cross-sensitization studies

Separate groups of rats (8–10 per group) received injections of fentanyl (0.016 mg/kg; s.c.) or nicotine (0.4 mg/kg, i.p.) once per day for 5 days in the colony room. Place conditioning sessions (morphine 5.0 mg/kg vs. saline) were conducted on days 8–9.

2.9. Opioid antagonist studies

Separate groups of animals (6–10 per group) received once daily injections of saline or the opioid receptor antagonist naloxone (0.1–0.5 mg/kg) 15 min prior to s.c. injections of morphine (5.0 mg/kg/day × 5 days). Place conditioning (morphine 5.0 mg/kg vs. saline) was then conducted on days 8–9. Additional animals received naloxone (0.5 mg/kg) 15 min prior to once daily injections of either fentanyl or nicotine (0.4 mg/kg) for 5 days. Morphine-induced place conditioning was then assessed as described above.

2.10. Statistical analysis

Conditioning scores represent the time spent in the drug-paired place minus that spent in the saline-paired place and are expressed as means ± S.E.M. The Wilcoxon test, in which time spent in the drug-paired place was compared to that spent in the saline-paired place was used to determine whether an individual dose produced significant place conditioning. A significant greater amount of time spent in the drug- as compared to vehicle-paired place was defined as a conditioned place preference. A two-factor (pretreatment vs. cocaine dose) analysis of variance (ANOVA) or, when appropriate, a single-factor ANOVA followed by the Dunnett's test was used to determine the effects of the various treatments upon morphine-induced place conditioning.

3. Results

In control tests of preference, animals which received saline during each of the conditioning sessions exhibited no preference for either of the place cues. The mean time spent in the black compartment minus that spent in the white compartment was: 10.2 ± 27 s (four sessions; $n = 6$) and −2.8 ± 24 s (six sessions; $n = 8$).

Fig. 1 shows the place conditioning produced by morphine in previously opioid-naive animals as a function of the dose of morphine administered and the number of conditioning sessions. Morphine (1.0–5.0 mg/kg) failed to produce significant conditioning in animals which received two conditioning sessions with drug. Thus, regardless of the dose of morphine used for conditioning, no preference for either of the place cues was seen. In contrast, animals which received three drug conditioning sessions exhibited a marked preference for the morphine-associated place. Significant place preferences were observed in response to doses of 3.0 mg/kg and higher. A two-factor ANOVA of these data indicated significant effects of morphine dose [$F(3,53) = 2.8$; $P \leq 0.05$] and number of conditioning sessions [$F(1,53) = 10.4$; $P \leq 0.002$] as well as a significant interaction effect [$F(3,53)2.7$; $P \leq 0.05$]. In view of these results, two drug conditioning sessions were employed for all subsequent studies.

Fig. 2 shows the place conditioning produced by graded doses of morphine in animals which had previously received once daily injections of morphine (5.0 mg/kg) for 5 days. Place conditioning commenced 3 days later. Morphine failed to produce significant place preferences in control animals after two conditioning sessions. In animals with a prior history of morphine administration, an enhanced response to morphine was seen. Thus, significant

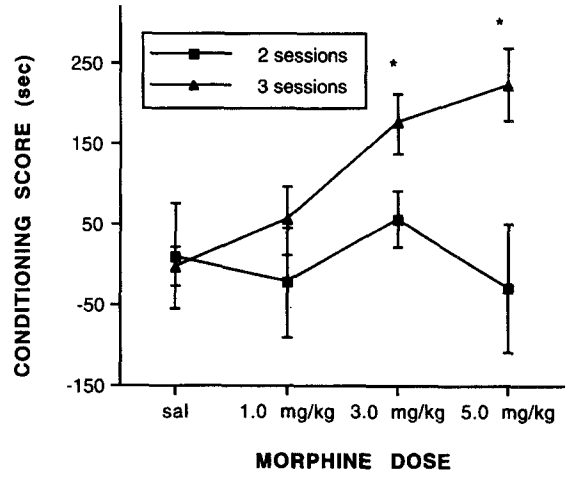

Fig. 1. Place conditioning produced by morphine in previously opioid naive animals. Animals received once daily injections of saline for 5 days in the colony room. The place conditioning produced by graded doses of morphine was assessed after either two or three conditioning sessions with drug. The dose of morphine used for conditioning is shown on the abscissa. Conditioning score defined as the time spent in the drug-paired place minus that spent in the saline place is shown on the ordinate. Saline (sal) data refer to animals which received saline during each of the conditioning sessions. Each data point represents the mean and S.E.M. of 6–10 rats. Asterisks denote significant place conditioning (Wilcoxon test).

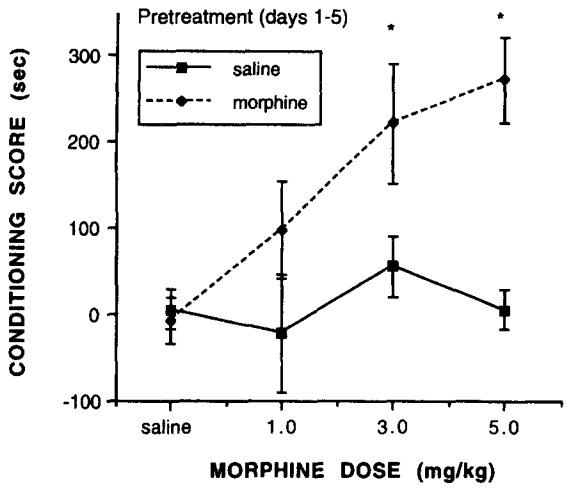

Fig. 2. Influence of prior morphine treatment upon morphine-induced place conditioning. Animals received once daily injections of either morphine (5.0 mg/kg; s.c.) or saline for 5 days. Place conditioning sessions (2 morphine; 2 saline) commenced 3 days later. Each data point represents the mean and S.E.M. of 6–10 rats. Asterisks denote significant place conditioniong (Wilcoxon test). The data from saline-pre-exposed animals is reproduced from Fig. 1.

place preferences were observed in response to morphine doses of 3.0 and greater. A two-factor ANOVA revealed a significant effect of pretreatment [$F(1,55) = 10.7$; $P \leq 0.002$] but no dose [$F(3,55) = 2.2$; $P \geq 0.1$] or interaction [$F(3,55) = 2.1$; $P \geq 0.12$] effects.

Fig. 3 shows the place conditioning produced by morphine (5.0 mg/kg) as a function of the interval between prior morphine treatment and the commencement of place conditioning. Significant preferences in response to morphine occurred when conditioning commenced either 3, 10 or 21 days after the cessation of the 5 day morphine

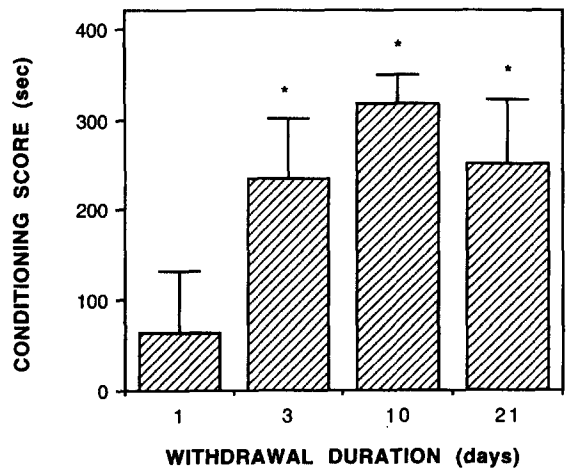

Fig. 3. Influence of withdrawal duration upon morphine-induced place conditioning. Animals received once daily injections of morphine (5.0 mg/kg) for 5 days. Place conditioing (2 morphine; 2 saline) commenced either 1, 3, 10 or 21 days following the cessation of the morphine treatment. The dose of morphine used for conditioning was 5.0 mg/kg. Each data point represents the mean and S.E.M. of 6–8 rats. Asterisks denote significant place conditioning (Wilcoxon test).

Table 1
Morphine-induced place conditioning in animals previously exposed to the μ-opioid receptor agonist fentanyl or the psychotimulant nicotine. Animals received once daily injections of fentanyl or nicotine for 5 days. Place conditioning sessions (2 morphine; 2 saline) commenced 3 days later. The dose of morphine used for conditioning was 5.0 mg/kg

Treatment (days 1–5)	Time (s)		Number of animals
	Drug-paired place	Saline-paired place	
Fentanyl (0.016 mg/kg)	406 ± 14 [a]	288 ± 20	9
Nicotine (0.4 mg/kg)	394 ± 20 [a]	219 ± 6	6

[a] Significant preference for the morphine-paired place.

treatment regimen. When, however, conditioning commenced 1 day after the cessation of the morphine treatment regimen, no enhanced response to morphine was seen. Thus, the conditioning score of these animals did not differ from those previously exposed to saline. An ANOVA of these data revealed a significant effect of time upon morphine-induced place conditioning [$F(3,26) = 4.1$, $P < 0.04$].

Table 1 shows the place conditioning produced by morphine in animals which had previously received the μ-opioid receptor agonist fentanyl or the psychostimulant, nicotine. Prior administration of either drug resulted in an enhanced response to morphine (5.0 mg/kg). Thus, the administration of morphine to these animals resulted in significant preferences for the drug-associated place.

The results of antagonist testing are shown in Fig. 4. ANOVA revealed a significant effect of naloxone treatment [$F(2,17) = 7.2$; $P \leq 0.006$]. Morphine produced significant place preferences in animals which had previously

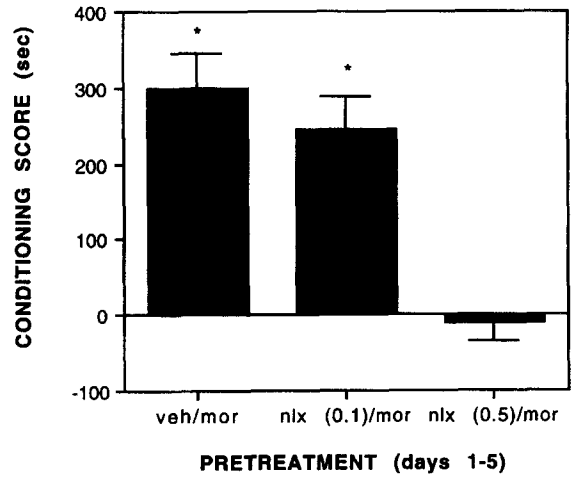

Fig. 4. Morphine-induced conditioning in animals which had previously received morphine in combination with naloxone. Animals received a daily injection of vehicle or naloxone (0.1–0.5 mg/kg) once each day for 5 days. Fifteen minutes later they received an s.c. injection of morphine (5.0 mg/kg). Place conditioning sessions (2 morphine; 2 saline) commenced 3 days later. The dose of morphine used for conditioning was 5.0 mg/kg. Each data point represents the mean and S.E.M. of 6–8 rats. Asterisks denote significant place conditioning (Wilcoxon test).

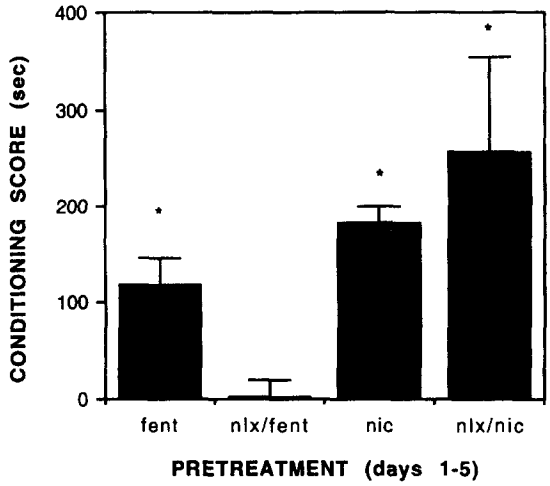

Fig. 5. Morphine-induced place conditioning in animals which had previously received fentanyl or nicotine in combination with naloxone. Animals received daily injections of naloxone once each day for 5 days. Fifteen minutes later, they received injections of either fentanyl (0.016 mg/kg) or nicotine (0.4 mg/kg). Place conditioning sessions (2 morphine; 2 saline) commenced 3 days later. The dose of morphine used for conditioning was 5.0 mg/kg. Each data point represents the mean and S.E.M. of 6–8 rats. Asterisks denote significant place conditioning (Wilcoxon test).

received the 5 day morphine treatment regimen in combination with naloxone (0.1 mg/kg). The magnitude of this effect did not differ from animals which had received morphine in combination with the naloxone vehicle. Administration of 0.5 mg/kg naloxone, however, prevented the enhanced response to morphine. Thus, the conditioning score of animals which received the morphine pretreatment in combination with this dose of naloxone did not differ from that of control (saline-pretreated) animals.

As shown in Fig. 5, naloxone (0.5 mg/kg) treatment was also effective in preventing the fentanyl-induced enhancement of morphine place conditioning. In contrast, such treatment failed to modify the effects of repeated nicotine administration. Thus, animals which had received naloxone in combination with nicotine (0.4 mg/kg) for 5 days exhibited significant place preferences in response to morphine and this effect did not differ from animals which received nicotine alone.

4. Discussion

The present study demonstrates that prior exposure to either morphine, fentanyl or nicotine results in an enhancement of the conditioned rewarding effects of morphine, i.e. sensitization. Administration of the opioid receptor antagonist, naloxone, prevented the sensitization produced by the prior administration of morphine and fentanyl. Such treatment did not modify the enhancement of morphine place conditioning produced by nicotine.

Control animals exhibited a marked preference for an environment associated with the administration of morphine. The magnitude of this effect varied as a function of the number of conditioning sessions employed as well as the dose of morphine administered. Thus, doses of morphine ranging from 1.0 to 7.5 mg/kg failed to produce significant place conditioning after two drug conditioning sessions. In contrast, after three sessions, a dose of 5.0 mg/kg resulted in marked preferences for the morphine-paired place. Such findings confirm those of other studies (Mucha and Herz, 1985; Mucha and Iversen, 1984) and demonstrate that the rewarding effects of opioid receptor agonists can be conditioned to environmental stimuli which have previously signaled their administration.

Prior administration of either morphine or fentanyl resulted in an enhancement of the conditioned reinforcing effects of morphine. Thus, morphine failed to produce place conditioning after two conditioning sessions in control animals. In animals, however, with a prior history of opioid administration, significant place preferences in response to morphine doses of 3.0 and 5.0 mg/kg were seen. Such findings confirm that the repeated administration of morphine can result in sensitization to its conditioned rewarding effects (Gaiardi et al., 1991; Lett, 1989). Furthermore, they indicate that sensitization can also be induced by another drug of the same pharmacological class.

Previous studies have shown that behavioral sensitization is long-lasting (Babbini et al., 1975; Bartoletti et al., 1983; see review: Stewart and Badiani, 1993). The results of time course studies are consistent with these findings. Thus, an enhanced response to morphine was apparent 3, 10 or 21 days after the cessation of the morphine treatment regimen. It was, however, not apparent when conditioning commenced 24 h after the cessation of morphine treatment. Such findings are noteworthy in that they demonstrate that a period of drug-withdrawal is necessary for the expression of behavioral sensitization. Furthermore, they highlight the importance of time-course data in studies of this kind. Thus, in a previous study (Shippenberg et al., 1988) conducted 24 h after the cessation of a 4 day morphine treatment regimen, tolerance rather than sensitization to the conditioned rewarding effects of morphine was seen.

The behavioral activating effects of morphine are increased following its repeated administration (Bartoletti et al., 1983; see reviews: Kalivas and Stewart, 1991; Stewart and Badiani, 1993). Therefore, it could be argued that the increased activity during morphine conditioning sessions and the resulting decrease in neophobia (see review: Carr et al., 1989) may have accounted for the enhanced response to morphine. This explanation is, however, unlikely since an augmented motor response to morphine is observed as little as 1 day after the cessation of repeated morphine treatment (Kalivas and Duffy, 1987; Shippenberg et al., 1989). At this time point, no evidence of sensitization to the conditioned reinforcing effects of morphine is seen.

Alternatively, the enhancement of morphine conditioning may be due to an increase in the number of drug exposures rather than to the development of behavioral sensitization. If, however, the number of exposures per se is critical for the development of sensitization, then a similar response to morphine should have been apparent 1 as well as 3, 10 and 21 days following the cessation of morphine treatment. The failure to observe such is incompatible with the pre-exposure hypothesis and indicates that the augmented response to morphine is adaptive in nature. Additional studies are, however, necessary to determine what role, if any, sensitization may play in the conditioned response to morphine which typically develops in drug-naive animals after three or more drug conditioning sessions (Mucha and Herz, 1985; Mucha and Iversen, 1984).

Administration of the opioid receptor antagonist, naloxone, prevented the effects of the morphine and fentanyl treatments. Thus, the conditioning score of animals which had received 0.5 mg/kg naloxone in combination with either opioid receptor agonist for 5 days did not differ from that of animals which were opioid-naive prior to the commencement of place conditioning. Such findings confirm that the effects of morphine and fentanyl are opioid receptor-mediated. Interestingly, a dose of naloxone (0.1 mg/kg) which antagonizes the behavioral and neurochemical effects of μ- but not δ-opioid receptor agonists (Longoni et al., 1991) failed to modify the enhanced response to morphine. Given that naloxone binds with only a slightly higher affinity to μ- as compared to δ-opioid receptors (Magnun et al., 1982; Takemori and Portoghese, 1984), such findings may indicate an involvement of multiple opioid receptor types in mediating the sensitization which develops in response to repeated morphine administration.

The repeated administration of cocaine or amphetamine can result in an augmented behavioral response to morphine (see reviews: Kalivas and Stewart, 1991; Stewart and Badiani, 1993). Evidence that the repeated administration of opioids can sensitize animals to the behavioral effects of psychostimulants has also been presented. The results of the present study demonstrate that an enhanced response to morphine can also be observed following administration of nicotine. The interaction of this agent with morphine cannot be attributed to a non-specific effect of prior drug exposure since the repeated administration of dopamine receptor agonists or κ-opioid receptor agonists is without effect (T.S. Shippenberg, unpublished observations). An involvement of opioid receptors is also unlikely since a sensitized response to morphine was observed in animals which had received nicotine in combination with naloxone.

At present, the neural substrates mediating the enhanced response to morphine observed in the present study remain unclear. The repeated administration of opioids as well as psychostimulants increases the activity of dopaminergic neurons projecting to the nucleus accumbens (see review: Kalivas and Stewart, 1991). This action is thought to contribute, at least in part, to the behavioral sensitization which develops to these agents following their repeated administration. An involvement of these same neurons in mediating the rewarding effects of these agents has also been suggested (see review: Di Chiara, 1995). Given that morphine and fentanyl as well as nicotine and amphetamine increase extracellular levels of dopamine within the nucleus accumbens (Imperato et al., 1986; Nissl et al., 1994), the possibility arises that this increase may underlie the enhanced response to morphine observed in this and previous place conditioning studies (Gaiardi et al., 1991; Lett, 1989). Studies assessing this issue are currently in progress.

In summary, the present study demonstrates that the conditioned rewarding effects of morphine are enhanced in animals with a prior history of opioid or psychostimulant administration. It is suggested that this enhanced response may contribute, at least in part, to the conditioned drug-craving which has been observed in former addicts following exposure to cues which have previously signaled drug administration (Childress et al., 1986; O'Brien et al., 1992).

Finally, it is important to note that withdrawal from opioids as well as psychostimulants is associated with dysphoria as well as depression and anxiety (Gawin and Kleber, 1986; Maurer and Vogel, 1967). These changes in affect can occur in the absence of any somatic signs of withdrawal and may play an important role in the drug relapse (see review: Markou et al., 1993). Therefore, additional studies are needed to determine whether the observed enhancement of drug-induced place conditioning observed in this and other studies (Gaiardi et al., 1991; Lett, 1989; Shippenberg and Heidbreder, 1995) reflects sensitization to the conditioned rewarding effects of these agents or the negative reinforcing effects of drug withdrawal.

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