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Sensitization to the conditioned rewarding effects of morphine and cocaine: differential effects of the κ-opioid receptor agonist U69593

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Abstract

The ability of the κ-opioid receptor agonist U69593 to attenuate the sensitization and cross-sensitization which develops to the conditioned rewarding effects of morphine and cocaine was examined using an unbiased place-preference conditioning procedure. The influence of U69593 treatment upon sensitization and cross-sensitization to cocaine was also assessed. Doses of morphine (1.0–5.0 mg kg^{-1}) which failed to produce a conditioned response in drug-naive rats produced marked preferences for the drug-paired place in animals which had previously received once daily injections of morphine (5.0 mg kg^{-1}; s.c.) or cocaine (10.0 mg kg^{-1}; i.p.) for 5 days. Morphine-induced place preferences also occurred in animals which had received morphine in combination with U69593 (0.04–0.32 mg kg^{-1}; s.c.) on either days 3–5 or 1–5 of the morphine treatment regimen. In contrast, morphine failed to produce significant conditioning in animals which had received U69593 with cocaine for 5 days. Doses of cocaine (1.0–5.0 mg kg^{-1}) which did not produce a conditioned response in naive rats produced preferences for the drug-paired place in animals which had received once daily injections of cocaine (10.0 mg kg^{-1} $day^{-1} \times 5$ days; i.p.) or morphine (5.0 mg kg^{-1} $day^{-1} \times 5$ days; s.c.). No enhancement of cocaine-induced conditioning occurred in animals which had received U69593 on days 3–5 or on days 1–5 of the five-day cocaine treatment. In animals, however, which had received U69593 with morphine for 5 days, an enhanced response to cocaine was still seen. These findings confirm that sensitization and cross-sensitization develop to the conditioned rewarding effects of cocaine and morphine. They also indicate that the ability of a κ-opioid receptor agonist to prevent the development of these sensitized responses depends on the sensitizing agent employed. U69593 prevents sensitization and cross-sensitization induced by cocaine, but does not modify morphine-induced sensitization or the cross-sensitization which develops to cocaine after morphine administration. Published by Elsevier Science B.V.

Keywords: Behavioral sensitization; Morphine; Cocaine; κ-Opioid receptor

1. Introduction

The rewarding effects of morphine and cocaine can be conditioned to environmental stimuli previously associated with their administration (Mucha et al., 1982; Nomikos and Spyraki, 1988). Evidence that these conditioned effects may play an important role in the maintenance of compulsive drug-seeking behavior has also been presented (Davis and Smith, 1975; Ehrman et al., 1992; Gawin and Kleber, 1986; McLellan et al., 1986; O'Brien et al., 1990).

Preclinical studies have shown that the conditioned rewarding effects of morphine and cocaine are enhanced following their repeated administration. Thus, doses of cocaine (Lett, 1989; Shippenberg and Heidbreder, 1995) or morphine (Gaiardi et al., 1991; Lett, 1989; Shippenberg et al., 1996b) which are ineffective as conditioning stimuli in drug-naive animals produce conditioned place preferences in animals previously exposed to either agent. Such findings indicate that sensitization (Lett, 1989; Gaiardi et al., 1991; Shippenberg et al., 1996b) and cross-sensitization (Lett, 1989; Shippenberg and Heidbreder, 1995) develop to the conditioned rewarding effects of these agents. Furthermore, as has been observed with other behaviors (Livezey et al., 1995; Pollock and Kornetsky, 1989), such sensitization is long-lasting (Gaiardi et al., 1991; Shippenberg and Heidbreder, 1995; Shippenberg et al., 1996b).

A recent study (Shippenberg et al., 1996a) has shown the selective κ-opioid receptor agonists, U69593

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[(5α,7α,8β)-(−)-*N*-methyl-*N*-(7-(1-pyrrolidinyl)1-oxaspiro(4,5)dec-8-yl)bezenacetamide] and U50488[(*trans*-(DL)-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]-benzeneacetamide)methane sulfonate hydrate], prevent the development of sensitization to the conditioned rewarding effects of cocaine. Thus, doses of cocaine which produced place preferences in animals with a prior history of cocaine administration failed to produce a conditioned response in animals which had received the cocaine treatment regimen in combination with κ-agonists. Other studies have shown that κ-opioid receptor agonists can also, when given in combination with cocaine, attenuate sensitization to the psychomotor stimulant effects of cocaine (Heidbreder et al., 1993, 1995) and prevent the elevation of extracellular dopamine levels within the nucleus accumbens (Heidbreder et al., 1996; Weiss et al., 1992) which occurs during abstinence from cocaine (Heidbreder and Shippenberg, 1994). These data demonstrate that the activation of κ-opioid receptors can prevent alterations in behavior and neurochemistry which occur as a consequence of repeated cocaine administration.

An involvement of κ-opioid receptor systems in the development of morphine dependence and sensitization has also been suggested. Administration of the κ-opioid receptor antagonist, nor-binaltorphimine, during the induction of morphine dependence increased physical as well as affective signs of withdrawal in rats (Spanagel et al., 1994). Sensitization to the motor-activating effects of a subsequent morphine challenge was also enhanced suggesting that endogenous κ-opioid receptor systems modulate the development of opioid dependence and sensitization (Spanagel and Shippenberg, 1993). Given these findings, the question arises as to whether the administration of κ-opioid receptor agonists attenuates the development of either of these phenomena. A previous study has shown that the selective κ-opioid receptor agonist, U50488, fails to modify the development of morphine-induced physical dependence (Fukagawa et al., 1989). However, the influence of κ-opioid receptor agonist treatment upon the sensitization or cross-sensitization which develops to the behavioral effects of morphine has not been examined.

Accordingly, the present place-conditioning studies examined whether the administration of the selective κ-opioid receptor agonist U69593 (Lahti et al., 1985) attenuates: (i) the sensitization which develops to the conditioned rewarding effects of morphine following its repeated administration, or (ii) the cross-sensitization which develops to this agent following the administration of the psychostimulant cocaine. The ability of U69593 to modify the cross-sensitization which develops to the conditioned rewarding effects of morphine following repeated cocaine administration was also assessed. U69593 was selected for use in these studies since this κ-opioid receptor agonist has previously been shown to modify sensitization to the behavioral effects of cocaine (Heidbreder et al., 1995; Shippenberg et al., 1996a)

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (Charles River, Wilmington, MA), 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: 0700) with food and water available ad libitum. They were housed in the colony for at least 1 week prior to the onset of place conditioning. 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 NIDA/NIH Intramural Research Program.

2.2. Apparatus

Place conditioning was conducted in 30 cm × 60 cm × 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 Plexiglas floor. For test sessions, the partition was raised 12 cm above the floor and a 5 cm × 2 cm 'neutral' steel mesh platform was inserted along the seam separating the two compartments.

2.3. Place conditioning

Place conditioning was conducted as previously described using an unbiased procedure (Shippenberg and Heidbreder, 1995). Sessions were conducted twice each day with a minimum of 6 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 45 min. Following drug administration, they were confined to the other compartment for 45 min. Treatment compartment was counterbalanced for each drug dose and the presentation order of saline and drug was alternated. Tests of conditioning were conducted one 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 drug- and saline-paired environments was then assessed by visual analysis of the video-recorded test session by an observer blind to the experimental treatments. All sessions were conducted under conditions of dim illumination (6–9 fc) with masking white noise present. Under these conditions, Sprague–Dawley rats exhibit no preference for either of the place cues (Shippenberg and Heidbreder, 1995).

2.4. Drugs

Cocaine hydrochloride and morphine sulfate were supplied by the Research Technology Branch of the National Institute on Drug Abuse (Rockville, MD, USA) and prepared in sterile saline. U69593 [(5α,7α,8β)-(−)-*N*-methyl-*N*-(7-(1-pyrrolidinyl)1-oxaspiro(4,5)dec-8-yl)benzenacetamide] was obtained from Research Biochemicals (Wayland, MA, USA) and dissolved in sterile water containing 20% propylene glycol. Cocaine was administered i.p. and the doses administered refers to the salt. Morphine and U69593 were administered s.c. and doses refer to the base weight. The volume of all injections was 1.0 ml kg^{-1}.

2.5. Induction of sensitization and cross-sensitization to morphine

Animals (5–10 per group) received once daily injections of saline (1.0 ml kg^{-1}; s.c.; i.p.), morphine (5.0 mg kg^{-1}; s.c.) or cocaine (10.0 mg kg^{-1}; i.p.) for 5 days in a room distinct from that where conditioning occurred. Place-conditioning sessions with morphine (1.0–5.0 mg kg^{-1}) and saline commenced 72 h later and were conducted on days 8–9. Tests of conditioning occurred on day 10, 24 h after the last conditioning session. Previous studies in our laboratory have shown that these treatments result in an enhancement of morphine- and cocaine-induced place conditioning (Shippenberg and Heidbreder, 1995; Shippenberg et al., 1996b).

2.6. Influence of systemic U69593 treatment upon the development of sensitization and cross-sensitization to morphine

Animals (8–10 per group) received once daily injections of morphine (5.0 mg kg^{-1}; s.c.) or cocaine (10.0 mg kg^{-1}; i.p.) on days 1–2. On days 3–5, the κ-opioid receptor agonist U69593 (0.16 mg kg^{-1}) was administered s.c. 15 min prior to these injections. This U69593 treatment regimen was employed since it was that previously shown to prevent sensitization to the conditioned rewarding effects of cocaine (Shippenberg et al., 1996a). Place conditioning (morphine: 5.0 mg kg^{-1}) commenced 72 h later and was conducted on days 8 and 9. Tests of conditioning were conducted on day 10.

For subsequent experiments, separate groups of rats (7–10 per group) received once daily injections of morphine (5.0 mg kg^{-1}) or cocaine (10.0 mg kg^{-1}; i.p.) on days 1–5. All injections were preceded by an s.c. injection of U69593 (0.04–0.32 mg kg^{-1}). U69593 was administered 15 min prior to morphine or cocaine. Conditioning and testing were conducted as described above.

2.7. Induction of sensitization and cross-sensitization to cocaine

Animals (5–10 per group) received once daily injections of saline (1.0 ml kg^{-1}), cocaine (10.0 mg kg^{-1}; i.p.) or morphine (5.0 mg kg^{-1}; s.c.) for 5 days in a room distinct from that where conditioning occurred. Place conditioning with cocaine (5.0–10.0 mg kg^{-1}) and saline commenced 72 h later and were conducted on days 8–9. Tests of conditioning were conducted on day 10.

2.8. Influence of systemic U69593 treatment upon the development of sensitization and cross-sensitization to cocaine

Animals (5–10 per group) received once daily injections of U69593 (0.04–0.16 mg kg^{-1}) 15 min prior to the administration of cocaine (10.0 mg kg^{-1}; i.p.) or morphine (5.0 mg kg^{-1}; s.c.) for 5 days. Place-conditioning sessions with cocaine (10.0 mg kg^{-1}) were then conducted as previously described. The doses of U69593 employed were in the range of those shown to prevent sensitization to cocaine when administered on days 1–5 or days 3–5 of the cocaine treatment regimen (Shippenberg et al., 1996a).

2.9. Statistical analysis

Each rat was assigned a conditioning score which represents the time spent in the drug-paired place minus that spent in the saline-paired place. The Wilcoxon paired-sample 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 two-factor (pretreatment vs. conditioning drug dose) analysis of variance (ANOVA) or, when appropriate, a single-factor ANOVA, followed by the Dunnet's test was used to determine differences in the effects of the various treatments upon subsequent place conditioning. The accepted level of significance for all tests was $P \leq 0.05$. The data are presented as mean conditioning score $\pm$ S.E.M.

3. Results

In control tests of preference, animals which had received saline in each of the compartments exhibited no preference for either of the place cues confirming the unbiased nature of the conditioning procedure employed. The mean time spent in the black and white compartments were: 306 $\pm$ 17 s and 299 $\pm$ 18 s, respectively. Similarly, animals which received once daily injections of either morphine, cocaine, or vehicle prior to the commencement of place conditioning exhibited no preference for either of the place cues (Fig. 1). Morphine (1.0–5.0 mg kg^{-1}; i.p.)

was ineffective in producing significant place conditioning in animals which had previously received five daily injections of saline. Thus, after four conditioning sessions (two morphine; two saline), no preference for the drug-paired place was seen. In contrast, animals which had previously received morphine (5.0 mg kg^{-1} $day^{-1} \times 5$ days) exhibited marked place preferences in response to the subsequent administration of this agent (Fig. 1). Significant place preferences were observed in response to doses of 3.0 and 5.0 mg kg^{-1}. An enhancement of morphine-induced place conditioning was also observed in animals which had previously received cocaine (10.0 mg kg^{-1} $day^{-1} \times 5$ days). The minimum dose of morphine producing a conditioned response in these animals was 3.0 mg kg^{-1}. A two-factor ANOVA of the data revealed a significant effect of prior drug treatment ($F(2,81) = 4.6$; $P \leq 0.01$) and conditioning drug dose ($F(3,81) = 3.3$; $P \leq 0.03$) but no interaction effects ($F(6,81) = 0.86$; $P \geq 0.5$).

Fig. 2 shows the place conditioning produced by morphine (5.0 mg kg^{-1}) in animals which had previously received morphine (days 1–5) in combination with the selective κ-opioid receptor agonist U69593 (0.16 mg kg^{-1}; days 3–5). Animals which had received morphine in combination with either U69593 or its vehicle exhibited significant place conditioning in response to the 5.0 mg kg^{-1} dose of morphine. There were no differences between groups in the magnitude of these effects ($F(1,17) = 0.03$; $P \geq 0.9$).

A significant conditioned place preference to morphine was also observed in animals which had previously received cocaine (10.0 mg kg^{-1}; days 1–5) in combination with vehicle. In animals, however, which had received cocaine (10.0 mg kg^{-1}; days 1–5) in combination with U69593 (0.16 mg kg^{-1}; days 3–5), morphine was ineffective as a conditioning stimulus (Fig. 2). Thus, in these animals, morphine failed to produce a preference for the drug-paired place. An ANOVA revealed a significant effect of the U69593 treatment ($F(1,16) = 5.4$; $P \leq 0.03$).

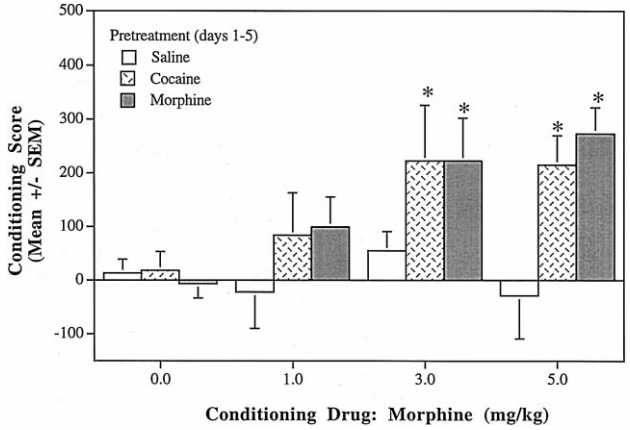

Fig. 1. Influence of prior morphine or cocaine administration upon the place conditioning produced by graded doses of morphine. Separate groups of animals received once daily injections of saline (1.0 ml kg^{-1}; s.c.), morphine (5.0 mg kg^{-1}; s.c.) or cocaine (10.0 mg kg^{-1}; i.p.) for 5 days in a room distinct from that where place conditioning was conducted. Place-conditioning sessions commenced 3 days later and were conducted on days 8–9. Tests of conditioning were conducted on day 10. Asterisks denote significant place conditioning (Wilcoxon test; $P \leq 0.05$).

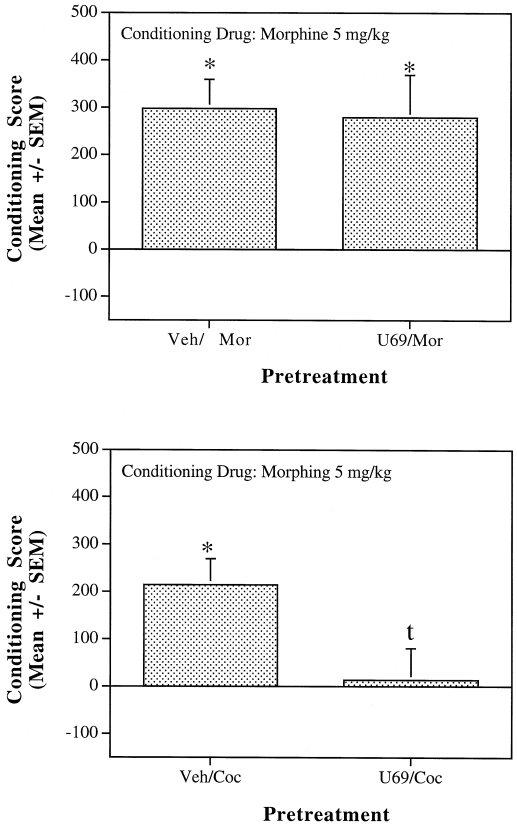

Fig. 2. Influence of U69593 upon the development of sensitization and cross-sensitization to morphine. Animals received once daily injections of morphine (5.0 mg kg^{-1} day^{-1}; upper panel) or cocaine (10.0 mg kg^{-1} day^{-1}; lower panel) on days 1–5. U69593 (0.16 mg kg^{-1}) or its vehicle was administered 15 min prior to morphine and cocaine on days 3–5 of the 5-day treatment regimen. Place-conditioning sessions (morphine 5.0 mg kg^{-1} vs. saline) commenced 3 days later and were conducted on days 8–9. Tests of conditioning were conducted on day 10. Asterisks denote significant place conditioning. [t]Denotes significant difference between the U69593 and vehicle treated groups (ANOVA; Dunnet's test; $P \leq 0.05$).

Additional studies were conducted to determine whether administration of U69593 throughout the 5-day morphine treatment regimen could modify the development of sensitization and cross-sensitization. Fig. 3 shows the place conditioning produced by morphine in animals which had previously received U69593 (0.04–0.32 mg kg^{-1}) throughout the 5-day morphine treatment regimen. Regardless of the dose of U69593 administered, no alteration in the conditioned response to morphine was seen ($F(3,31) = 0.4$; $P \geq 0.8$). Thus, morphine produced significant place preferences in animals which had previously received the five day morphine treatment regimen alone or always in combination with graded doses of U69593.

In animals which had received U69593 (0.16 mg kg^{-1} $day^{-1} \times 5$ days) in combination with cocaine for 5 days,

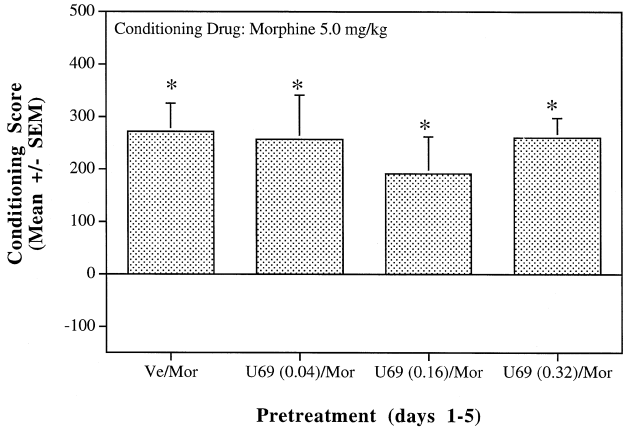

Fig. 3. Influence of graded doses of U69593 upon the development of morphine-induced sensitization. Animals received once daily injections of morphine (5.0 mg kg^{-1}; s.c.) in combination with U69593 (0.04–0.32 mg kg^{-1}; s.c.) or its vehicle on days 1–5 of the 5-day treatment regimen. Place-conditioning sessions (morphine 5.0 mg kg^{-1} vs. saline) commenced 3 days later and were conducted on days 8–9. Tests of conditioning were conducted on day 10. Asterisks denote significant place conditioning (Wilcoxon; $P \leq 0.05$).

the enhanced response to morphine was prevented. Thus, morphine produced a conditioning score of 214 ± 54 s ($n = 9$) in animals which had previously received vehicle in combination with cocaine for 5 days as compared to 26 ± 49 s ($n = 8$) in animals which had received U69593 with cocaine. An ANOVA revealed a significant difference between the U69593 and vehicle treated groups ($F(1,15) = 6.5$; $P \leq 0.02$).

Fig. 4 shows the place conditioning produced by cocaine (10.0 mg kg^{-1}) in control animals and those which had received cocaine (10.0 mg kg^{-1}) or morphine (5.0 mg kg^{-1}) for 5 days. Cocaine was ineffective as a conditioning stimulus in control animals after two drug-conditioning

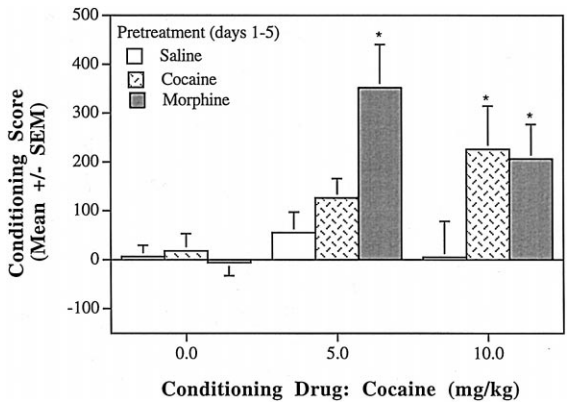

Fig. 4. Influence of prior morphine or cocaine administration upon the place conditioning produced by graded doses of cocaine. Separate groups of animals received once daily injections of saline (i.p.), morphine (5.0 mg kg^{-1}; s.c.) or cocaine (10.0 mg kg^{-1}; i.p.) for 5 days in a room distinct from that where place conditioning was conducted. Place-conditioning sessions commenced 3 days later and were conducted on days 8–9. Tests of conditioning were conducted on day 10. Asterisks denote significant place conditioning (Wilcoxon test; $P \leq 0.05$).

sessions. As however, reported previously (Shippenberg and Heidbreder, 1995), animals with a prior history of cocaine or morphine administration exhibited significant place preferences in response to cocaine. An ANOVA revealed a significant effect of prior drug treatment ($F(2,61) = 5.1$; $P \leq 0.009$) and conditioning drug dose ($F(2,61) = 4.7$; $P \leq 0.01$) but no interaction effect ($F(4,61) = 2.0$; $P \geq 0.1$).

Cocaine (10.0 mg kg^{-1}) failed to produce significant place conditioning in animals which had received the five day cocaine treatment regimen in combination with U69593 (0.04–0.16 mg kg^{-1}; Fig. 5, Shippenberg et al., 1996a). In animals, however, which had received the same doses of U69593 in combination with morphine for 5 days, significant conditioned place preferences in response to the 10.0 mg kg^{-1} dose of cocaine was seen (Fig. 5). An ANOVA of these data revealed that the magnitude of cocaine-in-

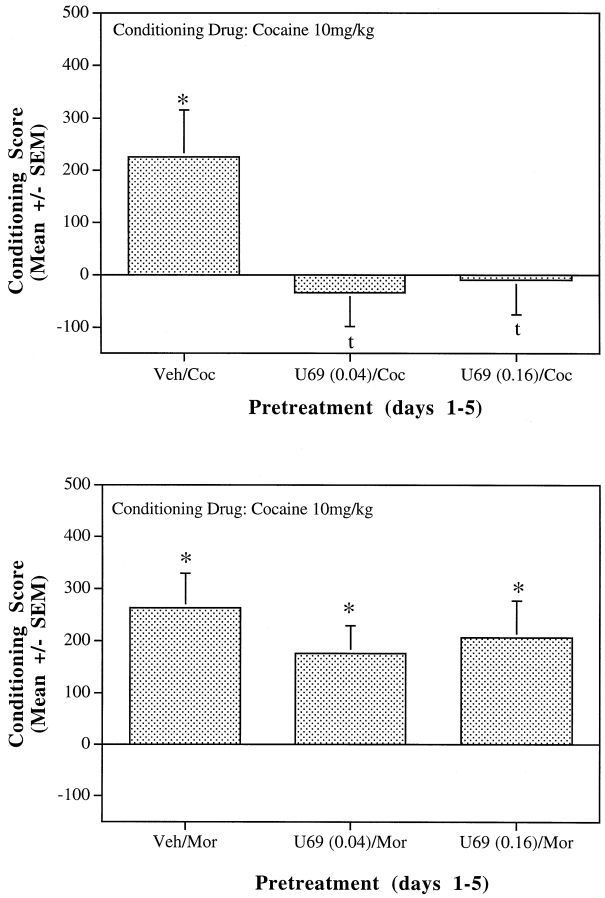

Fig. 5. Influence of U69593 upon the development of sensitization and cross-sensitization to cocaine. Separate groups of rats received once daily injections of cocaine (10.0 mg kg^{-1}; i.p.; upper panel) or morphine (5.0 mg kg^{-1}; s.c.; lower panel) in combination with U69593 (0.04–0.16 mg kg^{-1}; s.c.) or its vehicle on days 1–5 of the 5-day treatment regimen. Place conditioning sessions (cocaine 10.0 mg kg^{-1} vs. saline) commenced 3 days later and were conducted on days 8–9. Tests of conditioning were conducted on day 10. Asterisks denote significant place conditioning. ^{t}Denotes significant difference between the U69593- and vehicle-treated groups (ANOVA; Dunnet's test; $P \leq 0.05$).

duced place conditioning did not differ in animals which had received morphine in combination with vehicle or those that had received morphine in combination with U69593 ($F(2,23) = 0.42$; $P \geq 0.6$).

4. Discussion

The present study confirms that the conditioned rewarding effects of morphine and cocaine are enhanced following the repeated administration of these agents (e.g., sensitization) and that cross-sensitization also develops to the conditioned reinforcing effects of morphine and cocaine (Gaiardi et al., 1991; Lett, 1989; Shippenberg and Heidbreder, 1995; Shippenberg et al., 1996b). They demonstrate that the κ-opioid receptor agonist U69593 is ineffective in modifying the sensitization which develops to morphine following its repeated administration or the enhancement of cocaine-induced conditioning produced by the prior administration of morphine (e.g., cross-sensitization). In contrast, administration of a κ-opioid receptor agonist prevents cocaine-induced sensitization and the cross-sensitization which develops to morphine following the prior administration of cocaine.

Doses of morphine which were ineffective in producing place conditioning in drug-naive animals resulted in significant conditioned preferences for the drug-paired place in animals with a prior history of morphine administration. An enhanced conditioned response to morphine was also observed in animals with a prior history of cocaine administration. These findings add to a growing body of evidence which indicate that sensitization as well as cross-sensitization develop to the behavioral effects of opioids (see reviews: Kalivas and Stewart, 1991; Stewart and Badiani, 1993).

Administration of the selective κ-opioid receptor agonist U69593 (Lahti et al., 1985) failed to modify the sensitization which developed to morphine following its repeated administration. Thus, significant morphine-induced place conditioning was apparent in animals which received U69593 in combination with morphine either on days 3–5 or on days 1–5 of the 5-day morphine treatment regimen. Furthermore, the magnitude of this response did not differ from animals which had received morphine alone or in combination with the U69593 vehicle.

The doses of U69593 employed were those shown to be effective in other behavioral paradigms and to be selective for κ-opioid receptors (Shippenberg et al., 1988). They are also equal to or 3-fold greater than those which prevent sensitization to the behavioral effects of cocaine (Heidbreder et al., 1993, 1995) as well as the elevation of dialysate levels of dopamine which occur following the repeated cocaine administration (Heidbreder and Shippenberg, 1994). Therefore, the inability of this agent to modify the sensitized response to morphine can not be attributed to the U69593 treatment regimen employed.

The failure of U69593 treatment to modify the sensitized conditioned response to morphine is surprising in view of the documented role of endogenous κ-opioid systems in modulating other effects of morphine which occur as a consequence of its repeated administration. Thus, administration of the κ-opioid receptor antagonist, nor-binaltorphimine, exacerbates the sensitization which develops to the locomotor activating effects of morphine (Spanagel and Shippenberg, 1993) and increases the incidence of naloxone-precipitated withdrawal signs in morphine-dependent animals (Spanagel et al., 1994; Suzuki et al., 1992). Interestingly, however, Fukagawa et al. (1989) have shown that the development of morphine-induced physical dependence is not modified following the repeated administration of the selective κ-opioid receptor agonist, U50488H. These findings and those of the present study suggest that whereas a disruption in the activity of endogenous κ-opioid systems (e.g., dynorphin) exacerbates the development of opioid-induced sensitization and dependence, an increase in the functional activity of this system, as would occur following the administration of a selective agonist, is unable to prevent the development of either phenomenon.

U69593 treatment prevented the enhancement of morphine-induced place conditioning produced by the repeated administration of cocaine. Thus, doses of morphine which produced significant place preferences in animals which had previously received daily injections of cocaine (10.0 mg kg^{-1} $day^{-1} \times 5$ days) were ineffective in producing a conditioned response in animals which had received the same cocaine treatment regimen in combination with U69593. As such, these findings indicate that the effects of U69593 differ depending upon the sensitizing agent employed.

Previous studies (Lett, 1989; Shippenberg and Heidbreder, 1995) have demonstrated that the conditioned reinforcing effects of cocaine are enhanced in animals previously exposed to either cocaine or morphine. Sensitization and morphine-induced cross-sensitization to other behavioral effects of cocaine have also been reported (see reviews: Kalivas and Stewart, 1991; Stewart and Badiani, 1993). Recent data (Heidbreder et al., 1995; Shippenberg et al., 1996b) have shown that the administration of selective κ-opioid receptor agonists prevents the development of sensitization to the conditioned reinforcing and behavioral activating effects of cocaine. In the present study, U69593 treatment was ineffective in attenuating the enhancement of cocaine-induced place conditioning produced by morphine. Thus, animals which had previously received once daily injections of morphine in combination with U69593 exhibited significant place preferences in response to cocaine (10.0 mg kg^{-1}) and the magnitude of these effects did not differ from animals which had received the morphine treatment regimen in combination with the U69593 vehicle. The doses of U69593 employed were those which prevent the development of sensitization

to the conditioned rewarding and locomotor activating effects of cocaine (Heidbreder et al., 1993, 1995; Shippenberg et al., 1996a). They are also those, which when given in combination with cocaine, prevent cocaine-induced cross-sensitization to morphine. Taken together, these findings indicate that the effects of the κ-opioid receptor agonist, U69593, upon sensitization are specific to cocaine. U69593 prevents the development of cocaine-induced sensitization and cross-sensitization to morphine. In contrast, it fails to modify the morphine-induced sensitization and the cross-sensitization to cocaine which occurs following prior morphine administration. As such, these data indicate that distinct neuropeptide systems modulate psychostimulant as compared to opioid-induced sensitization and cross-sensitization.

The site and mechanism by which κ-opioid receptor agonists interact with cocaine are unclear. The acute administration of cocaine increases extracellular dopamine levels within the nucleus accumbens via an inhibition of the dopamine transporter (Hadfield and Nugent, 1983). Following the repeated administration of cocaine, the firing rate of dopamine neurons projecting to the nucleus accumbens is increased and dialysate levels of dopamine within the nucleus accumbens are elevated (Ackerman and White, 1990; Weiss et al., 1992). These alteration in mesolimbic neurotransmission are thought to contribute, at least in part, to the initiation of behavioral sensitization. Microdialysis studies (Di Chiara and Imperato, 1988; Spanagel et al., 1992) have shown that κ-opioid receptor agonists decrease extracellular dopamine levels within the nucleus accumbens via the activation of opioid receptors within this same brain region. κ-opioid receptor agonist administration also attenuates the increase in dialysate dopamine levels produced by the acute administration of cocaine (Maisonneuve et al., 1994). Such treatment also prevents the elevation of dopamine levels within the nucleus accumbens which occurs in response to the repeated administration of this psychostimulant (Heidbreder and Shippenberg, 1994). Therefore, these actions may underlie the abolition of cocaine-induced sensitization and cross-sensitization observed in the present study. Alternatively, two recent studies have shown that the repeated administration of a κ-opioid receptor agonist decreases the number of dopamine D_2 receptors within the nucleus accumbens and caudate putamen (Acri et al., 1996; Izenwasser et al., in press). Given the postulated role of dopamine D_2 autoreceptors in the initiation of sensitization (Ackerman and White, 1990), the possibility exists that dual sites of action may mediate the interaction of κ-opioid receptor agonists with cocaine. Finally, the repeated administration of cocaine, in contrast to morphine (Trujillo and Akil, 1991) is associated with a marked increase in prodynorphin gene expression within the nucleus accumbens (Hurd et al., 1992). Increases in κ-opioid receptor number and tissue levels of dynorphin have also been reported (Hurd and Herkenham, 1993; Unterwald et al., 1994). If, these alterations in the activity of endogenous κ-opioid systems are compensatory in nature, then the administration of κ-opioid receptor agonists, may by increasing the functional activity of this system, prevent long-term alterations in behavior and neurochemistry which occur in response to the repeated administration of cocaine.

In summary, the results of the present study demonstrate differential effects of the κ-opioid receptor agonist U69593 upon cocaine- as compared to morphine-induced sensitization and cross-sensitization. In view of the postulated roles of both sensitization and conditioning in the reinstatement of compulsive drug-seeking behavior (O'Brien et al., 1990; Robinson and Berridge, 1993), it is suggested that κ-opioid receptor ligands may be effective therapeutic agents for the treatment of cocaine but not opioid addiction.

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