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The δ-opioid receptor antagonist naltrindole prevents sensitization to the conditioned rewarding effects of cocaine

Toni S. Shippenberg *, Christian Heidbreder

Behavioral Pharmacol ogy and Genetics Section, NIDA Intramural Research Program, P.O. Box 5180, Baltimore, MD 21224, USA

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Abstract

A conditioned place preference paradigm was used to determine whether: (i) prior exposure to cocaine results in an enhancement of its rewarding effects, and (ii) the δ-opioid receptor antagonist naltrindole can prevent the development of this response. Rats received daily injections of saline or cocaine (10.0 mg/kg i.p.) for 5 days in the colony room. Additional animals received naltrindole (0.03–0.3 mg/kg s.c.), lithium chloride (20 mg/kg s.c.) or vehicle prior to i.p. injections. Conditioning sessions (2 drug; 2 vehicle) commenced 3 days later. Cocaine (1.0–10.0 mg/kg) was ineffective as a conditioning stimulus in saline pre-exposed rats. In cocaine pre-exposed animals, however, doses of 5.0 and 10.0 mg/kg cocaine resulted in significant drug-induced place preferences. Significant cocaine-induced place preferences were also observed in animals which had received lithium chloride with the cocaine treatment regimen. In animals which had received naltrindole together with the chronic cocaine treatment regimen, cocaine failed to produce a conditioned response. These data demonstrate that the repeated administration of cocaine results in an enhancement of its rewarding effects (e.g. sensitization) and that this phenomenon is prevented by a δ-opioid receptor antagonist. Furthermore, the finding that naltrindole does not modify the acute rewarding effects of cocaine suggests a specific role of δ-opioid receptors in the sensitization process.

Keywords: Cocaine; Naltrindole; Enkephalin; δ-Opioid receptor; Cocaine-induced sensitization

1. Introduction

A characteristic effect of cocaine and other drugs of abuse is their capacity to function as rewarding stimuli (Johanson and Fischman, 1989). This action underlies their abuse liability and leads to the initiation of compulsive drug-seeking behavior. Although the continued use of these agents is typically associated with the development of tolerance (Emmett-Oglesby and Lane, 1992; Stewart and Badiani, 1993), recent studies have shown that the repeated, intermittent administration of these agents can lead to an enhancement of their behavioral effects (Kalivas and Stewart, 1991; Kuczenski and Segal, 1988; Post, 1986). Such sensitization occurs within days after the cessation of drug use and is apparent for weeks or months thereafter. Evidence that the repeated administration of psychostimulants results in an enhancement of their rewarding effects has also been presented (Horger et al., 1990; Lett, 1989; Piazza et al., 1990) and it has been postulated that such sensitization may play an important role in drug-craving and the reinstatement of compulsive drug-seeking behavior (Robinson and Berridge, 1993). Accordingly, one focus of drug abuse research has been the identification of pharmacological treatments which can modify the development and/or expression of this phenomenon.

The acute administration of cocaine and other drugs of abuse increases extracellular dopamine levels within the nucleus accumbens (Di Chiara and Imperato, 1988), a terminal projection site of mesolimbic neurons. It is this action which is thought to underlie both their rewarding and locomotor activating effects (De Wit and Wise, 1977; Johanson and Fischman, 1989). Although the neural processes leading to sensitization are unclear, the repeated administration of psychostimulants such as cocaine is associated with an augmenta-

* Corresponding author. Tel. 1-410 550-1451, fax 1-410 550 1648.

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tion of basal dopamine release (Heidbreder and Shippenberg, 1994; Weiss et al., 1992) and an increase in the responsiveness of dopamine neurons to a subsequent drug challenge (Kalivas and Duffy, 1993; Kuczenski and Segal, 1988; Pettit et al., 1990). Such findings have led to the hypothesis that increased stimulation of dopamine receptors located within the nucleus accumbens and resulting alterations in the activity of postsynaptic output pathways may contribute, at least in part, to the induction of sensitization (Kalivas and Stewart, 1991; Stewart and Badiani, 1993).

Neurons containing enkephalin, the postulated endogenous ligand for the δ-opioid receptor (Davis et al., 1985) are located within the nucleus accumbens and comprise one output pathway of mesolimbic dopamine neurons (Finlay et al., 1981). The presence of δ-opioid receptors in the nucleus accumbens and other regions comprising the mesolimbic dopamine system has also been demonstrated (Mansour et al., 1987; Sesack and Pickel, 1992). It is well-documented that δ-opioid receptor agonists function as rewarding stimuli (Jenck et al., 1987; Phillips et al., 1983) and can modify mesolimbic dopamine neurotransmission (Pentney and Gratton, 1991; Spanagel et al., 1990). The existence of a tonically active enkephalin system which regulates basal dopamine release within the nucleus accumbens has also been suggested (Dauge et al., 1992; Giorgi et al., 1991). Several studies have shown that the acute administration of cocaine and other drugs which increase extracellular dopamine levels within the nucleus accumbens can modify proenkephalin gene expression as well as enkephalin levels within this same brain area (Bannon et al., 1989; Gerfen et al., 1990; Hurd and Herkenham, 1992; Taylor et al., 1991). A dramatic increase in gene expression has also been reported following the repeated self-administration of cocaine (Hurd et al., 1992). Such findings raise questions as to whether cocaine-induced increases in extracellular dopamine and subsequent alterations in the activity of enkephalin neurons modulate certain of the behavioral effects of cocaine.

Recently, we reported that the repeated administration of the selective δ-opioid receptor antagonist naltrindole (Portoghese et al., 1988a,b) prevents sensitization to the psychomotor stimulant effects of cocaine (Heidbreder et al., 1993). Although there are reports that δ-opioid receptor antagonists can modify the acute rewarding effects of cocaine (Bain and Kornetsky, 1987; Menkens et al., 1992; but see De Vries and Shippenberg, 1995; Negus et al., 1995), the role of enkephalin neurons in mediating the sensitization which develops to the rewarding effects of cocaine is unknown. Accordingly, the present study employed a conditioned place preference paradigm in rats to address this issue. Specifically we have sought to determine whether: (i) prior administration of cocaine can result in an enhancement of its conditioned rewarding effects, and (ii) the repeated administration of naltrindole can modify the development of this effect.

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 one week prior to the onset 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. Place conditioning procedure.

Place conditioning was conducted in 30 × 60 × 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 × 2 cm 'neutral' steel mesh platform was inserted along the seam separating the two compartments.

Conditioning was conducted as previously described using an unbiased procedure (Shippenberg et al., 1993). Conditioning sessions were conducted twice each day with a minimum of 6 h separating each. Rats were immediately confined to one compartment of the shuttlebox following administration of saline and to the other compartment following drug administration. Treatment compartment was counterbalanced for each drug dose and the presentation order of saline and the conditioning drug was alternated. All conditioning sessions were 45 min in duration. Tests of conditioning were conducted one day after the last conditioning session. For these, 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. All sessions were conducted under conditions of dim illumination (8.5–9.5 lux) with masking white noise present. Preliminary studies revealed that under these conditions, Sprague-

Dawley rats exhibit no preference for either of the place cues.

2.3. Naltrindole-induced place conditioning

The place conditioning produced by saline and graded doses of naltrindole (0.03–0.3 mg/kg s.c.) was evaluated in previously drug-naive animals. Animals were placed in one distinct environment following injections of naltrindole. Following injections of vehicle, they were placed in the other environment. A total of 8 sessions (4 drug; 4 vehicle) were conducted over 4 days. Tests of conditioning were conducted 24 h later.

2.4. Influence of prior cocaine administration upon cocaine-induced place conditioning

Animals received once-daily injections of saline or cocaine (10.0 mg/kg i.p.) for 5 days (days 1–5) in the colony room. Place conditioning commenced 3 days later and was conducted on days 8 and 9. During each of these days, animals received one conditioning session with saline and one with cocaine (1.0–10.0 mg/kg i.p.). A total of 4 conditioning sessions (2 cocaine; 2 saline) were conducted. Tests of conditioning were conducted on day 10.

2.5. Influence of prior naltrindole + cocaine administration upon cocaine-induced place conditioning

Animals received five daily injections of naltrindole (0.03–0.3 mg/kg s.c.) or its vehicle in the colony room. Fifteen minutes later, they received an injection of cocaine (10.0 mg/kg i.p.) or saline. Conditioning (saline vs. cocaine 10.0 mg/kg) sessions commenced 3 days later and were conducted on days 8–9. A total of 4 sessions were conducted.

2.6. Influence of prior lithium chloride + cocaine treatment upon cocaine-induced place conditioning

In view of the results obtained in Expt. 3, studies assessing the influence of another psychoactive drug upon the development of sensitization to cocaine were conducted. Separate groups of animals received five daily injections of cocaine (10 mg/kg) or saline in the colony room. Fifteen minutes prior to these injections they received an s.c. injection of lithium chloride (20 mg/kg) or saline. Conditioning sessions (saline vs. cocaine 10 mg/kg) were conducted as previously described on days 8–9. The dose of lithium chloride employed was that previously shown to produce aversive effects in rats (Shippenberg et al., 1988).

2.7. Cocaine-induced place conditioning in drug-naive animals: effects of naltrindole

Animals which were drug-naive prior to the commencement of place conditioning received four conditioning sessions with cocaine (5.0 and 10.0 mg/kg i.p.) and four with saline. The minimum dose producing significant place conditioning was then determined. Based on these data, a dose of 10 mg/kg cocaine was used to examine the cocaine-induced conditioning in animals which received naltrindole (0.1 mg/kg s.c.) prior to each conditioning session. Naltrindole or its vehicle were administered 15 min prior to i.p. injections of cocaine (10.0 mg/kg i.p.) and saline. Animals were placed in the conditioning apparatus immediately after the i.p. injections.

2.8. 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. The Wilcoxon matched pairs 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. cocaine dose) analysis of variance (ANOVA) or, when appropriate, a single-factor ANOVA was used to determine the effects of the various treatments upon cocaine-induced place conditioning. The Dunnett's test was used to determine whether the various treatment regimens produced effects different from that observed in control animals. The accepted level of significance for all tests was $P \leq 0.05$.

2.9. Drugs

Cocaine hydrochloride (NIDA) and saline were administered i.p. in a volume of 1.0 ml/kg. Naltrindole hydrochloride (RBI Corp., Wayland, MA, USA) and lithium chloride (Sigma, St. Louis, MO, USA) were dissolved in sterile water and administered via the s.c. route.

Table 1
Place conditioning produced by naltrindole

Naltrindole dose (mg/kg)	Time (s) drug-paired place	Time (s) saline-paired place	Conditioning score (mean ± S.E.)
0.03	249 ± 12	318 ± 46	−68 ± 52
0.1	293 ± 18	256 ± 45	+37 ± 36
0.3	352 ± 37	280 ± 17	+73 ± 52

Animals received 4 drug- and 4-saline conditioning sessions. Tests of conditioning occurred 24 h later. Each data point represents the mean ± S.E. of 6–8 rats.

3. Results

In control tests of preference, animals conditioned with saline failed to exhibit a preference for either of the place cues confirming that the conditioning procedure employed was of the unbiased type. The mean time spent in the black and white environments was 304 ± 29 and 286 ± 16 s, respectively. The place conditioning produced by naltrindole is shown in Table 1. As can be seen, naltrindole was ineffective as a conditioning stimulus. Thus, regardless of the dose of naltrindole administered, animals exhibited no preference for either the drug- or saline-paired place.

Cocaine was ineffective as a conditioning stimulus in animals which had received a total of four conditioning sessions (2 cocaine; 2 saline). Thus, in saline-preexposed animals, doses of 1.0–10.0 mg/kg failed to produce preferences for either the drug- or saline-paired place (Fig. 1). In contrast, animals with a prior cocaine history exhibited a marked preference for the cocaine-paired place. In these animals, doses of 5.0 and 10.0 mg/kg resulted in significant place conditioning. A two-factor ANOVA of these data revealed a significant effect of prior drug history ($F(1,43) = 4.8$; $P \leq 0.03$) but no dose ($F(2,43) = 1.0$; $P = 0.36$) or interaction ($F(2,43) = 0.3$; $P = 0.3$) effects.

The place conditioning produced by cocaine (10.0 mg/kg) in animals which had previously received the cocaine pretreatment regimen in combination with either naltrindole or its vehicle for 5 days is shown in Fig. 2. Prior administration of cocaine in combination with the naltrindole vehicle resulted in significant place conditioning and the magnitude of this effect did not differ from that observed previously. In animals, however, which had previously received naltrindole and cocaine for 5 days, no significant place conditioning in response to cocaine 10 mg/kg was seen. An ANOVA revealed a significant effect of prior drug treatment upon subsequent place conditioning ($F(3,28) = 4.4$; $P \leq 0.01$). The influence of prior lithium chloride treatment upon cocaine-induced conditioning is shown in Fig. 3. As recently reported (Shippenberg and Heidbreder, 1995), animals which received the cocaine pre-

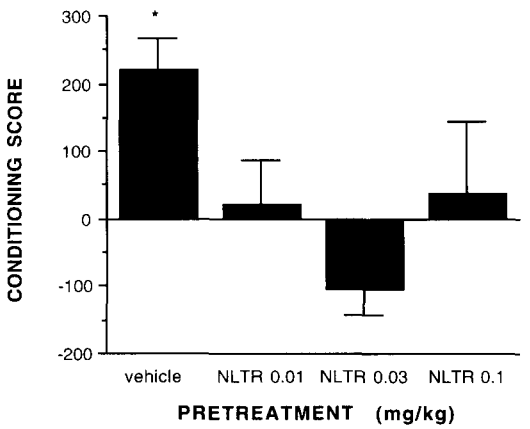

Fig. 2. Influence of prior naltrindole + cocaine treatment upon cocaine-induced place conditioning. Animals received s.c. injections of naltrindole or its vehicle in combination with cocaine on days 1–5. Place conditioning produced by cocaine (10.0 mg/kg) was subsequently evaluated. A total of 4 (2 cocaine; 2 saline) conditioning sessions were conducted on days 8–9. Tests of conditioning were conducted on day 10. Asterisks indicate significant place conditioning. Each point represents the mean ± S.E. of 7–10 rats.

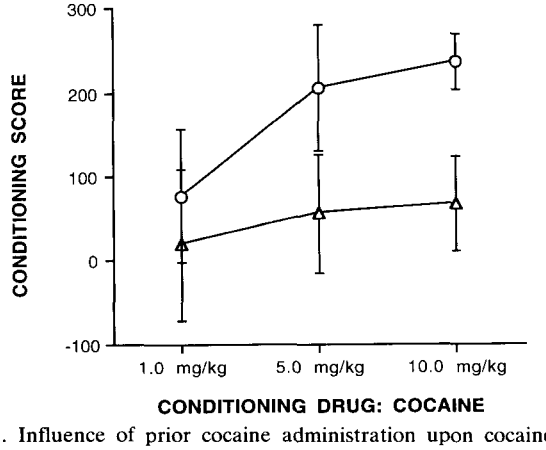

Fig. 1. Influence of prior cocaine administration upon cocaine-induced place conditioning. Animals received i.p. injections of saline or cocaine on days 1–5. Place conditioning produced by graded doses of cocaine was subsequently evaluated. A total of 4 (2 cocaine; 2 saline) conditioning sessions were conducted on days 8–9. Tests of conditioning were conducted on day 10. Asterisks indicate significant place conditioning. Each point represents the mean ± S.E. conditioning score of 6–10 rats. (△) Saline pre-exposed animals. (○) Cocaine pre-exposed animals.

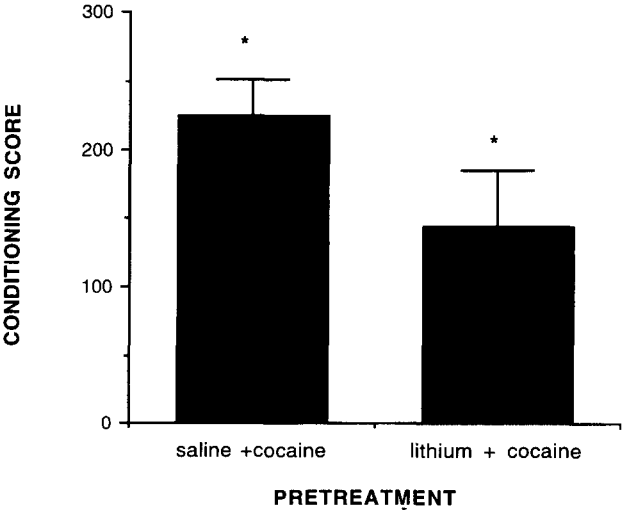

Fig. 3. Influence of prior lithium chloride + cocaine treatment upon cocaine-induced place conditioning. Animals received s.c. injections of lithium chloride (20.0 mg/kg) or vehicle in combination with cocaine on days 1–5. Place conditioning in response to cocaine (10.0 mg/kg) was then assessed. Conditioning sessions were conducted as described in the legend to Fig. 2. Each point represents the mean ± S.E. of 9 rats.

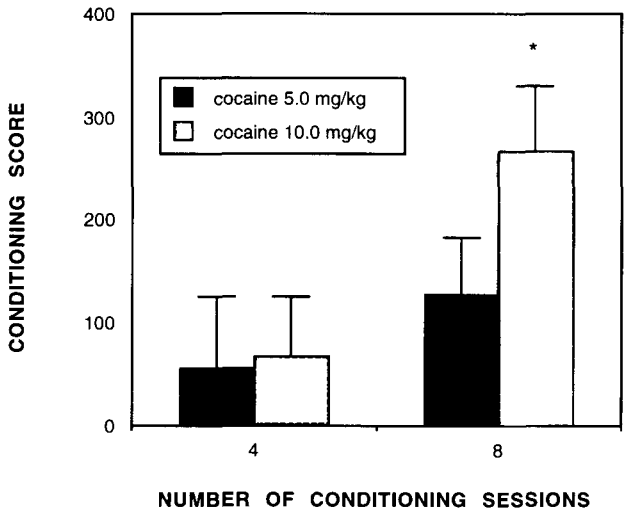

Fig. 4. Cocaine-induced place conditioning in previously drug-naive rats. Place-conditioning produced by cocaine (5.0 and 10.0 mg/kg) was assessed after a total of 4 (reproduced from Fig. 1) or 8 conditioning sessions. Asterisks denote significant place conditioning. Each point represents the mean ± S.E. of 8–10 rats.

treatment regimen in combination with lithium chloride exhibited a significant place preference in response to 10.0 mg/kg cocaine and the magnitude of this effect did not differ from controls (cocaine-preexposed) animals ($F(1,16) = 2.5$; $P \geq 0.13$).

Fig. 4 shows the place conditioning produced by 5.0 and 10.0 mg/kg cocaine in previously naive animals after a total of 8 conditioning sessions. In contrast to the 5.0 mg/kg dose of cocaine which was ineffective as a conditioning stimulus, administration of 10.0 mg/kg cocaine resulted in a significant preference for the drug-paired place. As shown in Table 2, animals which were conditioned with cocaine (10.0 mg/kg) in combination with naltrindole (0.1 mg/kg) also exhibited a significant place reference for the drug-paired place and the magnitude of this effect did not differ from animals which were conditioned with cocaine or cocaine in combination with the naltrindole vehicle.

Table 2
Place conditioning produced by cocaine (10.0 mg/kg)

Conditioning drug	Time (s) drug-paired place	Time (s) saline-paired place	Conditioning score (mean ± S.E.)
Vehicle + cocaine	418 ± 45	227 ± 37	+179 ± 73
Naltrindole + cocaine	444 ± 38	267 ± 27	+156 ± 63

Animals received naltrindole (0.1 mg/kg; $n = 8$) or saline ($n = 10$) prior to saline and cocaine conditioning sessions. A total of 8 (4 cocaine; 4 saline) conditioning sessions were conducted.

4. Discussion

In the present study, prior administration of cocaine resulted in an enhancement of its conditioned rewarding effects. Thus, after a total of four conditioning sessions, doses of cocaine ranging from 1.0 to 10.0 mg/kg were ineffective as conditioning stimuli in saline pre-exposed animals. In animals, however, previously exposed to cocaine, doses as low as 5.0 mg/kg resulted in significant drug-induced place preferences. Such findings are in agreement with those of recent studies (Lett, 1989; Shippenberg and Heidbreder, 1994, 1995) and confirm that the prior administration of cocaine results in sensitization to its conditioned rewarding effects.

Animals which had previously received the cocaine treatment regimen in combination with the opioid receptor antagonist naltrindole failed to exhibit an enhanced response to cocaine. Thus, in these animals, a dose of 10.0 mg/kg cocaine failed to produce significant place conditioning. Naltrindole binds with high affinity to the δ-opioid receptor and is postulated to be a selective ligand for this opioid receptor type (Portoghese et al., 1988a,b). Therefore, the ability of this antagonist to prevent the enhanced response to cocaine suggests an important role of δ-opioid receptors in modulating the development of cocaine-induced sensitization. In this regard, it is important to note that the doses of naltrindole which produced this effect are those which result in the selective blockade of δ-opioid receptors (Kitchen and Pinker, 1990). Furthermore, they are 100-fold lower than those previously shown to attenuate the rewarding effects associated with the acute administration of cocaine (Menkens et al., 1992; Reid et al., 1993).

It may be suggested that the interaction of naltrindole with cocaine observed in the present study was behavioral rather than pharmacodynamic in origin. That is, the presence of another drug during the preexposure phase may merely have masked the unconditioned effects of cocaine and, thus, prevented the development of sensitization to this agent. If such was the case, than other drugs given in combination with the cocaine pretreatment regimen should also prevent the enhanced response to cocaine. The finding that lithium chloride, in a dose previously shown to produce conditioned place aversions (Shippenberg et al., 1988), fails to modify the development of sensitization to cocaine strongly suggests that this is not the case.

Alternatively, it may be argued that the effects of naltrindole observed in the place preference paradigm may reflect an antagonist-induced attenuation of the motoric effects of cocaine rather than an effect upon reward processes per se. Indeed, we have recently shown that the administration of naltrindole attenuates the sensitization which develops to the locomotor acti-

vating effects of cocaine (Heidbreder et al., 1993). If, such was the case, however, then other drug treatments which attenuate sensitization to the motoric effects of cocaine should prevent sensitization to the rewarding effects of cocaine. However, dopamine D_2 receptor antagonists which attenuate sensitization to the motoric effects of cocaine (Fontana et al., 1993; Mattingly et al., 1994) are ineffective in modifying the enhancement of cocaine-induced place conditioning produced by prior cocaine exposure (Shippenberg and Heidbreder, 1994, 1995). Taken together, such finding strongly indicate that the effects of naltrindole are pharmacodynamic in origin.

The administration of cocaine to drug-naive animals also resulted in significant preferences for the drug-paired place. However, this effect was only observed when the number of conditioning sessions was increased from four to eight. Such findings are in accord with previous place conditioning studies (Morency and Beninger, 1986) and confirm that cocaine can function as a rewarding stimulus in drug-naive animals. Furthermore, they demonstrate that the magnitude of drug-induced place conditioning can vary depending on the number of conditioning sessions as well as the dose of drug employed.

In contrast to its effects upon sensitization, naltrindole failed to modify the acute rewarding effects of cocaine. Thus, animals which received naltrindole (0.1 mg/kg) prior to each conditioning session exhibited marked place preferences in response to cocaine and the magnitude of this effect did not differ from that of control animals. As noted previously, the dose of naltrindole employed was that shown to result in the blockade of δ- but not μ-opioid receptors (Kitchen and Pinker, 1990). It was also that which was maximally effective in preventing sensitization to the conditioned reinforcing effects of cocaine. Therefore, the inability of naltrindole to modify cocaine-induced place conditioning in naive animals suggests that the rewarding effects of cocaine occur independently of δ-opioid receptor activation. Indeed, recent self-administration studies suggest that this may, in fact, be the case (De Vries and Shippenberg, 1995; Negus et al., 1995). Furthermore, the finding that doses of naltrindole which prevent sensitization to other behavioral effects of cocaine (Heidbreder et al., 1993) fail to modify those effects associated with their acute administration (De Vries and Shippenberg, 1995; Heidbreder and Shippenberg, unpublished observations; Jones et al., 1993) suggests the specific involvement of δ-opioid receptors in modulating those effects of cocaine which result from its repeated administration.

At present, the site and mechanism by which naltrindole prevents sensitization to the rewarding effects of cocaine is unclear. Given, however, the postulated role of mesolimbic dopamine neurons in the sensitization process (Kalivas and Stewart, 1991) and the existence of a tonically active δ-opioidergic system which modulates the activity of these neurons (Dauge et al., 1992; Giorgi et al., 1991), studies examining the involvement of this system in mediating the interaction of naltrindole with cocaine appear warranted.

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