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Differential role of δ-opioid receptors in the development and expression of behavioral sensitization to cocaine

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Abstract

The present study was designed to determine whether the selective δ-opioid receptor antagonist naltrindole hydrochloride can prevent the expression and development of sensitization to the locomotor-activating effects of cocaine. Rats were sensitized to the motor stimulant effects of cocaine (20 mg/kg i.p. × 3 days). 48 h after withdrawal of pretreatment, rats were pretreated with naltrindole (0.1–1.0 mg/kg s.c.) or its vehicle and 15 min later challenged with either saline or the sensitizing dose of cocaine. In a second set of experiments, naltrindole (0.1–1.0 mg/kg s.c.) or its vehicle were given in combination with either saline or cocaine (20 mg/kg i.p.) for 3 days. Activity in response to saline and to cocaine (20 mg/kg i.p.) was assessed on days 4 and 5, respectively. Additional experiments determined whether naltrindole prevents the development of sensitization to the locomotor-activating effects of nicotine: naltrindole (0.3, 1.0 mg/kg s.c.) or its vehicle were given in combination with nicotine (0.6 mg/kg s.c.) for 3 days. Naltrindole blocked the development but not expression of sensitization to the locomotor-activating effects of cocaine. In contrast, naltrindole failed to modify nicotine-induced sensitization in nicotine-treated animals. These data suggest that δ-opioid receptors are involved in the development but not expression of behavioral sensitization to cocaine.

Keywords: Cocaine; Enkephalin; δ-Opioid receptor; Naltrindole; Sensitization

1. Introduction

The repeated and intermittent administration of psychoactive drugs can result in an enhancement of their locomotor-activating effects (for a review, see Kalivas and Barnes, 1993). This persistent phenomenon, referred to as sensitization, is thought to play a major role in maintaining compulsive drug use and in being responsible, at least in part, for the reinstatement of drug-seeking behaviors in drug addicts after periods of abstinence (Kalivas et al., 1993; Robinson, 1993; Robinson and Berridge, 1993).

It is now well established that the acute administration of psychostimulants increases extracellular dopamine levels within the nucleus accumbens (Di Chiara and Imperato, 1988a; Kalivas and Duffy, 1990), one of the terminal projection fields of the mesolimbic dopamine system originating in the ventral tegmental area. This effect has been suggested to mediate both the locomotor-activating effects and rewarding properties of these drugs (Wise and Bozarth, 1987).

Repeated administration of cocaine enhances the responsitivity of dopamine neurons to a subsequent drug challenge and it has been postulated that this increase is critical for the development of the sensitization process (Kalivas and Duffy, 1990, 1993). Recent studies support the idea that it is an enhanced basal dopamine tone in the nucleus accumbens which may, in fact, be critical for the initiation of behavioral sensitization to cocaine (Weiss et al., 1992; Heidbreder and Shippenberg, 1994).

There is a growing body of evidence to support an opioid modulation of the mesolimbic dopamine system. Populations of μ-, δ-, and κ-opioid receptors have been identified on mesolimbic dopamine neurons (Mansour et al., 1987). Enkephalin-immunoreactive fibers are detected in the ventral tegmental area (Khachaturian et al., 1985) and appear to originate in the nucleus accumbens and ventral pallidum (Groenewegen and Russchen, 1984). In common with μ-opioid receptor agonists, δ-opioid recep-

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tor agonists increase extracellular dopamine levels in the nucleus accumbens (Di Chiara and Imperato, 1988b; Spanagel et al., 1992). The effects of both μ- and δ-opioid receptor agonists on dopamine overflow result from the activation of their respective receptors in the ventral tegmental area (Spanagel et al., 1992; Devine et al., 1993). Evidence has also been reported for the involvement of ventral tegmental area μ- and δ-opioid receptors in producing forward locomotion (Latimer et al., 1987; Calenco-Choukroun et al., 1991), opioid self-administration (Devine and Wise, 1990), and conditioned preferences for environments associated with prior drug exposure (Bals-Kubik et al., 1990). Furthermore, a tonic control of mesolimbic dopamine neurotransmission by endogenous enkephalins is suggested by results obtained with enkephalinases inhibitors (Giorgi et al., 1991; Daugé et al., 1992).

Various studies have demonstrated that manipulations of dopamine neurotransmission can regulate the expression of opioid peptides and opioid receptors. More specifically, dopamine depletion or neuroleptic treatment enhances enkephalin mRNA and peptide levels in striatopallidal neurons (Gerfen et al., 1990, 1991; Li et al., 1990). Cocaine treatment elevates striatonigral dynorphin content (Sivam, 1989; Smiley et al., 1990) and striatal prodynorphin mRNA levels (Spangler et al., 1993; Hurd et al., 1992). Repeated systemic injection of cocaine also produces an upregulation of μ-opioid receptors in various mesolimbic areas including the nucleus accumbens (Unterwald et al., 1994). These findings raise questions as to whether manipulations of the endogenous opioidergic system can modify some of the behavioral effects of non-opioid drugs such as cocaine.

Several studies reported that the δ-opioid receptor antagonist naltrindole (Portoghese et al., 1988) is able to attenuate the behavioral effects of cocaine and amphetamine (Jones and Holtzman, 1992; Menkens et al., 1992; Reid et al., 1993; Jones et al., 1993). Recently, we revealed that naltrindole prevents the development of sensitization to both the locomotor-activating and conditioned rewarding effects of cocaine (Heidbreder et al., 1993; Shippenberg and Heidbreder, 1995). In the present study, we further examined the influence of acute and repeated administration of the δ-opioid receptor antagonist naltrindole upon the motor activity induced either by acute or repeated cocaine treatments. Additional studies were also undertaken to determine whether naltrindole modifies the locomotor-activating effects of another psychostimulant, nicotine.

2. Materials and methods

2.1. Subjects

Male Sprague-Dawley rats (Charles River, Wilmington, MA) weighing 280–310 g were housed three per cage in a temperature- and humidity-controlled environment under a 12-h light/dark cycle. Food and water were available ad libitum. Rats were handled for 1 week prior to beginning experiments. All rats were experimentally naive and separate animals were used for each drug and dose tested. Animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and all experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Addiction Research Center, National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication (NIH) 85-23, revised 1985.

2.2. Measurement of spontaneous locomotor activity

Six photocell chambers (Auto-Track System, Columbus, OH, USA) were operated simultaneously with an

Table 1
Experimental groups assessing the effects of acute administration of naltrindole on cocaine-induced locomotor activity in saline- and cocaine-pretreated rats [a]

Pretreatment [×3 days]	Acute administration (s.c.)	Challenge (i.p.)
Saline (1.0 ml/kg i.p.)	Naltrindole vehicle (1.0 ml/kg)	Saline (1.0 ml/kg) Cocaine (20 mg/kg)
Saline (1.0 ml/kg i.p.)	Naltrindole (0.1–1.0 mg/kg)	Saline (1.0 ml/kg) Cocaine (20 mg/kg)
Cocaine (20 mg/kg i.p.)	Naltrindole vehicle (1.0 ml/kg)	Saline (1.0 ml/kg) Cocaine (20 mg/kg)
Cocaine (20 mg/kg i.p.)	Naltrindole (0.1–1.0 mg/kg)	Saline (1.0 ml/kg) Cocaine (20 mg/kg)

[a] Rats were habituated to the photocell chambers for 50 min after which time they received a s.c. injection of naltrindole (0.1–1.0 mg/kg), or its vehicle. They were returned immediately to the same apparatus for 15 min and were then challenged with either saline (1.0 ml/kg i.p.) or cocaine (20 mg/kg i.p.).

IBM-PC computer as the data acquisition and storage unit. Each chamber was composed of Plexiglas monitor cages (40 × 40 × 35 cm) surrounded by 15 emitters and phototransistors positioned in both the horizontal and vertical planes. These sensors directed infrared beams throughout the monitor cage. The distance between each beam was 2.4 cm. The distance traveled represents the distance traveled (cm) by one animal in a chamber during a particular recording period (10 min). The animal's location was read by the Auto-Track system 10 times each second. The distance traveled was calculated from the last reported location of the animal using the Pythagorean theorem (Sanberg et al., 1985).

When rats were tested in the monitoring device, they were habituated to the chambers for 50 min after which time they received either an i.p. injection of saline (1.0 ml/kg) (saline challenge) or an i.p. injection of cocaine (20 mg/kg i.p.) (cocaine challenge). They were then returned immediately to the same apparatus where locomotor activity was assessed for 100 min.

Each experimental group contained six rats, and assignment of these rats to the six activity chambers was counterbalanced across all groups.

2.3. Experimental design

The experiments were designed to examine the influence of various doses of the selective δ-opioid receptor antagonist naltrindole hydrochloride upon the locomotor activity produced by cocaine and nicotine, and the sensitization which develops to these drugs following their repeated administration.

2.3.1. Influence of naltrindole on the expression of sensitization to cocaine (Table 1)

In a first set of experiments, rats were sensitized to the locomotor-activating effects of cocaine. The following injection regimen was employed: days 1–3, saline (1.0 ml/kg s.c.) was administered 15 min prior to cocaine (20 mg/kg i.p.) or saline. 48 h after withdrawal of sensitization treatment, each group of rats was pretreated with naltrindole (0.1, 0.3, 1.0 mg/kg s.c.) or its vehicle and 15 min later challenged with either saline (1.0 ml/kg i.p.) or the sensitizing dose of cocaine (20 mg/kg i.p.).

2.3.2. Influence of naltrindole on the development of sensitization to cocaine (Table 2)

In a second set of experiments, naltrindole (0.1, 0.3, 1.0 mg/kg s.c.) or its vehicle (1.0 ml/kg s.c.) were given in combination with saline (1.0 ml/kg i.p.) or cocaine (20 mg/kg i.p.) for 3 days. On day 4, activity in response to a saline challenge (1.0 ml/kg i.p.) was assessed in the photocell apparatus. On day 5, activity in response to a cocaine challenge (20 mg/kg i.p.) was monitored in the same photocell apparatus.

2.3.3. Influence of naltrindole on the development of sensitization to nicotine (Table 2)

In a third set of experiments, naltrindole (0.3, 1.0 mg/kg s.c.) or its vehicle (1.0 ml/kg s.c.) were given in combination with nicotine (0.6 mg/kg s.c.). Daily pretreatments and assessment of locomotor activity were conducted as described above.

2.4. Data analysis

Data from experiment 1 were analyzed using a four-way (pretreatment [saline + saline vs. saline + cocaine] × challenge dose of cocaine [0 vs. 20 mg/kg i.p.] × acute dose of naltrindole [0; 0.1; 0.3; 1.0 mg/kg s.c.] × time) analysis of variance (ANOVA) with repeated measures over time.

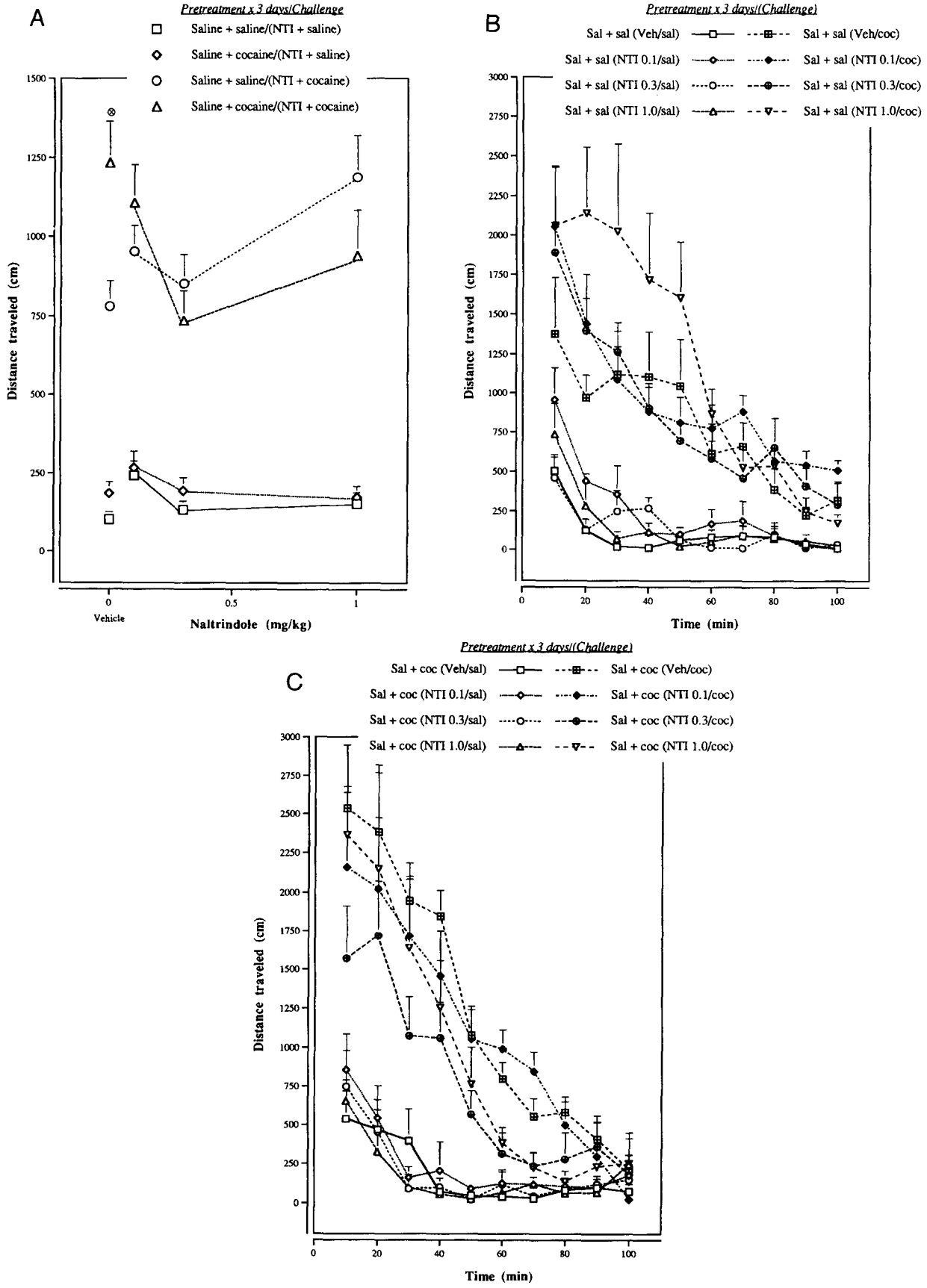
Data from experiment 2 were analyzed using a four-way (pretreatment [saline vs. cocaine] × repeated dose of naltrindole [0; 0.1; 0.3; 1.0 mg/kg s.c.] × challenge dose of cocaine [0 vs. 20 mg/kg i.p.] × time) analysis of variance (ANOVA) with repeated measures over time.

Data from experiment 3 were analyzed using a four-way (pretreatment [saline vs. nicotine] × repeated dose of nal-

Table 2
Experimental groups assessing the effects of repeated administration of naltrindole on cocaine- and nicotine-induced locomotor activity [b]

Repeated administration (days 1–3)	Challenge, day 4	Challenge, day 5
Naltrindole vehicle + saline	Saline (1.0 ml/kg)	Cocaine (20 mg/kg)
Naltrindole vehicle + cocaine (20 mg/kg)	Saline (1.0 ml/kg)	Cocaine (20 mg/kg)
Naltrindole (0.1–1.0 mg/kg) + saline	Saline (1.0 ml/kg)	Cocaine (20 mg/kg)
Naltrindole (0.1–1.0 mg/kg) + cocaine (20 mg/kg)	Saline (1.0 ml/kg)	Cocaine (20 mg/kg)
Naltrindole vehicle + saline	Saline (1.0 ml/kg)	Nicotine (0.6 mg/kg)
Naltrindole vehicle + nicotine (0.6 mg/kg)	Saline (1.0 ml/kg)	Nicotine (0.6 mg/kg)
Naltrindole (0.3–1.0) + nicotine (0.6 mg/kg)	Saline (1.0 ml/kg)	Nicotine (0.6 mg/kg)

[b] 24 h after daily treatment for 3 days, rats were habituated to the photocell apparatus for 50 min after which time they received an i.p. injection of saline (saline challenge). On day 5, rats were challenged with an i.p. injection of either cocaine (20 mg/kg) (cocaine challenge) or nicotine (nicotine challenge). Locomotor activity was assessed for 100 min after the challenge injections.


A
Pretreatment x 3 days/Challenge
Saline + saline/(NTI + saline)
Saline + cocaine/(NTI + saline)
Saline + saline/(NTI + cocaine)
Saline + cocaine/(NTI + cocaine)
Distance traveled (cm)
Vehicle
Naltrindole (mg/kg)
B
Pretreatment x 3 days/(Challenge)
Sal + sal (Veh/sal)
Sal + sal (Veh/coc)
Sal + sal (NTI 0.1/sal)
Sal + sal (NTI 0.1/coc)
Sal + sal (NTI 0.3/sal)
Sal + sal (NTI 0.3/coc)
Sal + sal (NTI 1.0/sal)
Sal + sal (NTI 1.0/coc)
Distance traveled (cm)
Time (min)
C
Pretreatment x 3 days/(Challenge)
Sal + coc (Veh/sal)
Sal + coc (Veh/coc)
Sal + coc (NTI 0.1/sal)
Sal + coc (NTI 0.1/coc)
Sal + coc (NTI 0.3/sal)
Sal + coc (NTI 0.3/coc)
Sal + coc (NTI 1.0/sal)
Sal + coc (NTI 1.0/coc)
Distance traveled (cm)
Time (min)

trindole [0; 0.3; 1.0 mg/kg s.c.] × challenge dose of nicotine [0 vs. 0.6 mg/kg s.c.] × time) analysis of variance (ANOVA) with repeated measures over time.

For each data set, post-hoc analysis was performed, when appropriate, using the Student-Newman-Keuls' range test for multiple comparisons. After confirmation of main effects or interactions by the overall ANOVAs, contrasts were defined to compare the means of selected levels of a factor, or combination of factors. The accepted level of significance for all test was $P \leq 0.05$.

2.5. Drugs

Drugs administered systemically were cocaine hydrochloride (NIDA, Baltimore, MD, USA), nicotine hydrogen tartrate salt (Sigma Chemicals, St Louis, MO, USA), and the selective δ-opioid receptor antagonist naltrindole hydrochloride. Cocaine HCl and nicotine were dissolved in saline 0.9%; naltrindole hydrochloride (RBI Corp., Wayland, MA, USA) or its vehicle (10% dimethylsulfoxide) were administered s.c. 15 min prior to i.p. injections. All injections were conducted in the home cage in a different room from where locomotor activity was assessed.

3. Results

3.1. Effect of acute administration of graded doses of naltrindole upon cocaine-induced locomotor activity in drug-naive and cocaine-experienced rats

Fig. 1A shows the locomotor activity of saline- and cocaine-pretreated animals which received naltrindole (0.1–1.0 mg/kg s.c.) 15 min prior to a challenge injection of saline (1.0 ml/kg i.p.) or cocaine (20 mg/kg i.p.). As can be seen, acute administration of naltrindole did not modify the distance traveled in response to either saline or cocaine. A four-way ANOVA revealed a significant effect of challenge dose ($F(1,80) = 141.0$; $P < 0.0001$), and time ($F(9/720) = 91.9$; $P < 0.0001$), but no significant effect of pretreatment ($F(1,80) = 0.1$; $P = 0.7$), and naltrindole dose ($F(3,80) = 1.5$; $P = 0.2$), as well as no interaction between pretreatment × challenge dose of cocaine × naltrindole dose × time ($F(27,720) = 0.9$; $P = 0.5$). Time course data are shown in Fig. 1B (saline pretreatment) and 1C (cocaine pretreatment).

3.2. Effect of repeated administration of naltrindole on cocaine-induced locomotor activity in saline- and cocaine-pretreated rats

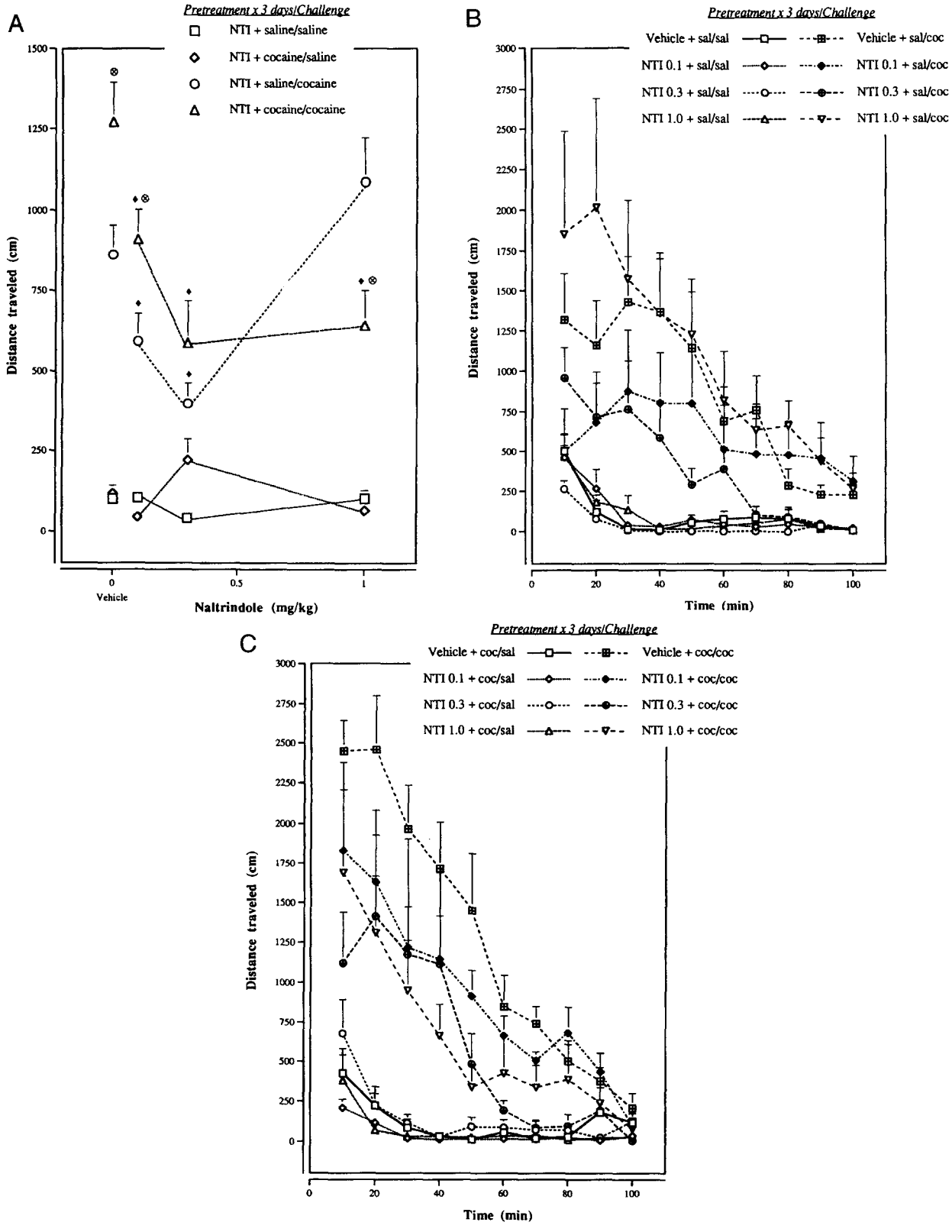
Naltrindole (0.1–1.0 mg/kg s.c.) treatment for 3 days did not modify the distance traveled in response to a subsequent saline challenge. Administration of cocaine (20 mg/kg i.p.) to saline-pretreated animals significantly increased locomotor activity relative to a saline challenge. Naltrindole pretreatment attenuated the stimulatory effects of cocaine (Fig. 2A). Both the 0.1 and 0.3 mg/kg dose of naltrindole prevented the acute locomotor-activating effects of cocaine. In contrast, the highest dose of naltrindole tested (1.0 mg/kg) failed to produce any significant effect. Time course data are shown in Fig. 2B. Fig. 2A also depicts the influence of naltrindole pretreatment upon the development of sensitization to the locomotor-stimulating effects of cocaine. Daily injections of cocaine produced an enhanced motor response to cocaine. Naltrindole (0.1–1.0 mg/kg s.c.) significantly reduced this effect. Maximal inhibition was observed with a dose of 0.3 mg/kg whereas a higher dose (1.0 mg/kg) resulted in less of an effect. Time course data are seen in Fig. 2C. A four-way ANOVA revealed significant effects of naltrindole dose ($F(3,80) = 2.7$; $P < 0.04$), challenge dose ($F(1,80) = 95.6$; $P < 0.0001$), and time ($F(9,720) = 49.02$; $P < 0.0001$), but no significant interaction ($F(27,720) = 1.2$; $P = 0.2$).

3.3. Effect of repeated administration of naltrindole on nicotine-induced locomotor activity in nicotine-pretreated rats

Administration of nicotine (0.6 mg/kg s.c.) to saline-pre-exposed animals significantly increased locomotor activity. The repeated administration of nicotine (0.6 mg/kg s.c.) for 3 days resulted in a sensitized motor response to a subsequent nicotine challenge (Fig. 3). When given in combination with nicotine (0.6 mg/kg s.c.), naltrindole (0.3–1.0 mg/kg s.c.) failed to modify locomotor activity in response to a saline challenge (Fig. 4A). The magnitude of the sensitized motor response to a nicotine challenge did

Fig. 1. Effect of acute administration of the δ-opioid receptor antagonist naltrindole on locomotor activity in rats pretreated with either saline or cocaine. Rats received a single injection of naltrindole (0.1–1.0 mg/kg s.c.) or its vehicle 15 min prior to an i.p. challenge injection of either saline (1.0 ml/kg) or cocaine (20 mg/kg). Panel A: the data represent the mean distance traveled (cm) by the animals for 100 min following a saline (1.0 ml/kg i.p.) or a cocaine (20 mg/kg i.p.) challenge. Each point represents the mean ± S.E.M. of 6 rats. $^{\otimes}$ $P < 0.05$ vs. saline + saline/(NTI-cocaine) according to a four-way (pretreatment × challenge dose of cocaine × naltrindole dose × time) ANOVA with repeated measures over time followed by the Student-Newman-Keuls' range test for multiple comparisons and analysis of contrasts to compare the means of selected levels of a factor, or combination of factors. Panel B: the data represent the time course of panel A and show the effect of acute administration of naltrindole on distance traveled following a saline or a cocaine (20 mg/kg i.p.) challenge in rats previously treated with saline for 3 days. Panel C: the data represent the time course of panel A and show the effect of acute administration of naltrindole on distance traveled following a saline or a cocaine (20 mg/kg i.p.) challenge in rats previously treated with cocaine (20 mg/kg i.p.) for 3 days.

not differ from animals which had received naltrindole (0.3–1.0 mg/kg s.c.) in combination with nicotine (Fig. 4A). Time course data are shown in Fig. 4B. A four-way ANOVA revealed no significant effect of naltrindole dose ($F(2,30) = 0.24$; $P = 0.8$) or any interaction ($F(22,330) = 0.6$; $P = 0.9$), but did reveal significant effects of nicotine



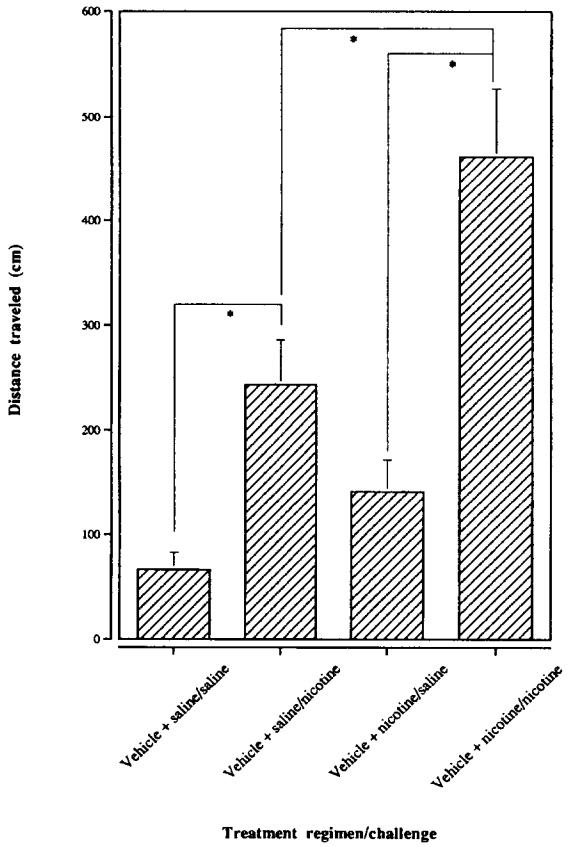


Fig. 3. Effect of repeated administration of nicotine on nicotine-induced locomotor activity in saline- and nicotine-pretreated rats. Rats were pretreated for 3 days with one daily injection of naltrindole vehicle given in combination with either saline or nicotine (0.6 mg/kg s.c.). The data represent the mean distance traveled (cm) by the animals for 100 min following a saline (1.0 ml/kg i.p.) or a nicotine (0.6 mg/kg s.c.) challenge. Each column represents the mean ± S.E.M. of 6 rats. * $P < 0.05$ according to a two-way (pretreatment × time) ANOVA with repeated measures over time followed by the Student-Newman-Keuls' range test for multiple comparisons and analysis of contrasts to compare the means of selected levels of a factor, or combination of factors.

dose ($F(1,30) = 20.2$; $P < 0.0001$), challenge dose ($F(3,20) = 9.6$; $P < 0.0004$), and time ($F(11,330) = 35.3$; $P < 0.0001$).

4. Discussion

Acute administration of cocaine to drug-naive animals produced an increase in locomotor activity. Sensitization to the locomotor-activating effects of cocaine was observed following its repeated administration. A single injection of naltrindole failed to modify the locomotor-activating effects of cocaine in either saline- or cocaine-pretreated animals. In contrast, the prior repeated administration of naltrindole for 3 days significantly reduced the motor response to a subsequent cocaine challenge in both saline- and cocaine-treated rats. Sensitization to the locomotor stimulant effects of nicotine was not modified by repeated administration of naltrindole.

Our results demonstrate that, although no sensitized motor responses were observed in animals which had received naltrindole in combination with the cocaine treatment regimen, acute administration of naltrindole in cocaine-pretreated rats did not modify cocaine sensitization. The fact that repeated naltrindole treatment blocked the development of sensitization to the locomotor-activating effects of cocaine seem to implicate δ-opioid receptors in the long-term neural changes underlying the sensitization process. The data of this experiment further indicate that δ-opioid receptors do not seem to be involved in the expression of sensitization to cocaine. The mechanisms by which repeated naltrindole treatment modifies the motor-stimulant effects of cocaine are unclear. The repeated administration of cocaine has been shown to result in an enhancement of its motoric effects (Kalivas and Stewart, 1991). Such sensitization is associated with increased basal dopamine release in the nucleus accumbens (Weiss et al., 1992; Heidbreder and Shippenberg, 1994) and enhanced dopamine overflow in response to a subsequent cocaine challenge (Kalivas and Duffy, 1990, 1993; but see Weiss et al., 1992). There is also evidence to suggest that the activity of endogenous opioid systems is altered in response to repeated cocaine administration (Hurd et al., 1992; Steiner and Gerfen, 1993; Spangler et al., 1993). Cocaine and the dopamine uptake inhibitor GBR 12909 both increase enkephalin mRNA in the striatum and it has

Fig. 2. Effect of repeated administration of graded doses of naltrindole on cocaine-induced locomotor activity in saline- and cocaine-pretreated rats. Rats were pretreated for 3 days with one daily injection of either naltrindole (0.1–1.0 mg/kg s.c.) or its vehicle 15 min prior to the injection of saline or cocaine (20 mg/kg i.p.). Panel A: the data represent the mean distance traveled (cm) by the animals for 100 min following a saline (1.0 ml/kg i.p.) or a cocaine (20 mg/kg i.p.) challenge. Each point represents the mean ± S.E.M. of 6 rats. ⊗ $P < 0.05$ vs. NTI + saline/cocaine); ♦ $P < 0.05$ vs. Vehicle according to a four-way (pretreatment × challenge dose of cocaine × naltrindole dose × time) ANOVA with repeated measures over time followed by the Student-Newman-Keuls' range test for multiple comparisons and analysis of contrasts to compare the means of selected levels of a factor, or combination of factors. Panel B: the data represent the time course of panel A and express distance traveled following a saline or a cocaine (20 mg/kg i.p.) challenge in rats previously treated with naltrindole given in combination with saline for 3 days. Panel C: the data represent the time course of panel A and express distance traveled following a saline or a cocaine (20 mg/kg i.p.) challenge in rats previously treated with naltrindole given in combination with cocaine (20 mg/kg i.p.) for 3 days.

been suggested that this effect involves a dopamine D_2 component (Hurd and Herkenham, 1992). Indeed, activation of dopamine D_1 receptors results in decreased enkephalin levels, whereas activation of dopamine D_2 receptors gives rise to an increase in the enkephalin response (Takada and Hattori, 1986; Taylor et al., 1991). Thus, one may assume that cocaine, by inhibiting dopamine re-uptake in the nucleus accumbens, predominantly activates dopamine D_2 receptors and, consequently, increases enkephalin levels. Endogenous enkephalins have been shown to produce behavioral effects in the mesolimbic system through preferential stimulation of δ-opioid receptors (Calenco-Choukroun et al., 1991; Daugé et al., 1988). Increased enkephalin levels, in turn, may have sensitized δ-opioid receptors in the nucleus accumbens and repeated administration of naltrindole in combination with cocaine would have prevented the development of these sensitized responses.

It is interesting to note that naltrindole became less selective as the dose increased. Indeed, high doses of naltrindole have been demonstrated to block μ- as well as δ-opioid receptors. It has been shown, for example, that 2.0 mg/kg naltrindole is able to antagonize the release of corticosterone induced by the selective μ-opioid receptor agonist, fentanyl (Kitchen and Kennedy, 1990). Such findings suggest that a low dose of naltrindole may still produce μ-opioid receptor antagonist effects. Furthermore, some μ- and δ-opioid receptors may exist in a μ/δ-opioid receptor complex (Holaday et al., 1985) such that activation of δ-opioid receptors could affect the effects produced by stimulation of μ-opioid receptors.

Repeated administration of naltrindole failed to modify the sensitization which develops to nicotine following its repeated administration. At present, an explanation for the interaction of naltrindole with cocaine but not nicotine is unclear. The locomotor-activating effects of acutely administered nicotine, like cocaine, has been attributed to an increase in extracellular dopamine levels within the nucleus accumbens (Clarke et al., 1988; Museo and Wise, 1990). There is, however, evidence suggesting that the site of action of these agents may differ. Thus, the locomotor-activating and dopamine-releasing effects of nicotine have been attributed to a stimulation of dopamine cell firing occurring at the level of the ventral tegmental area (Museo and Wise, 1990; Nisell et al., 1994; Reavill and Stolerman, 1990). In contrast, the effects of cocaine are presumed to occur at the level of the nucleus accumbens via an inhibition of dopamine re-uptake (Hadfield and Nuggent, 1983).

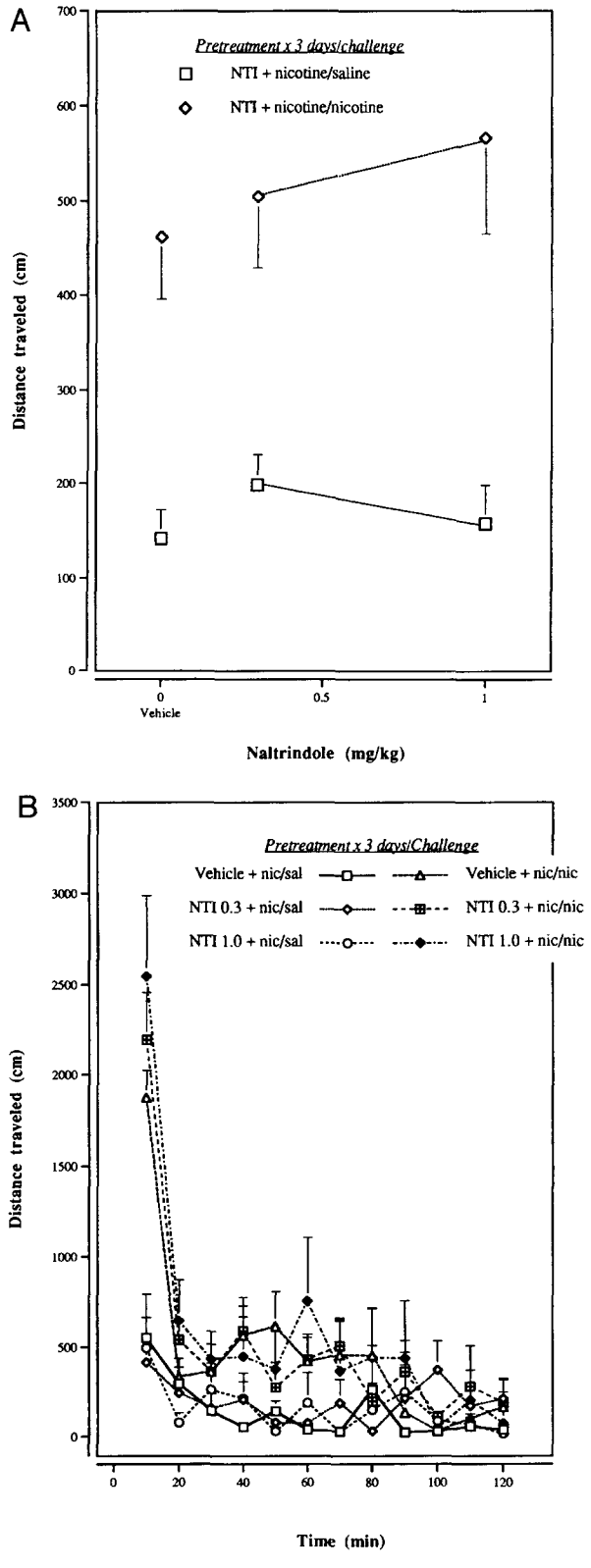


Fig. 4. Effect of repeated administration of naltrindole on nicotine-induced locomotor activity in nicotine-pretreated rats. Rats were pretreated for 3 days with one daily injection of either naltrindole (0.3–1.0 mg/kg s.c.) or its vehicle 15 min prior to the injection of nicotine (0.6 mg/kg s.c.). Panel A: the data represent the mean distance traveled (cm) by the animals for 100 min following a saline (1.0 ml/kg i.p.) or a nicotine (0.6 mg/kg s.c.) challenge. Each point represents the mean ± S.E.M. of 6 rats. Panel B: the data represent the time course of panel A and express the distance traveled following a saline or a nicotine (0.6 mg/kg s.c.) challenge in rats previously treated with naltrindole given in combination with nicotine for 3 days.

It has been shown that, contrary to the nucleus accumbens, the ventral tegmental area has a low density of δ-opioid receptors (Mansour et al., 1987; Tempel and Zukin, 1987). These differences in density and regional specificity may account for the differential efficacy of naltrindole in modifying sensitization to the behavioral effects of nicotine and cocaine. Furthermore, it is important to note that, whereas sensitization to cocaine is typically associated with an enhancement of mesolimbic dopamine neurotransmission (Kalivas and Duffy, 1993), sensitization to the motoric effects of nicotine is not (Damsma et al., 1989).

In conclusion, the present data demonstrate that naltrindole blocked the development but not the expression of sensitization to the locomotor-activating effects of cocaine. In contrast, naltrindole failed to modify nicotine-induced sensitization in nicotine-treated animals. Doses of naltrindole in the range of 0.5–1.0 mg/kg have been reported to selectively antagonize δ-opioid receptor-mediated behaviors in rats (Jackson et al., 1989; Kitchen and Pinker, 1990). Thus, the dose regimen (0.1–1.0 mg/kg naltrindole) employed further indicates that the effects observed in the present study are specific to a blockade of δ-opioid receptors. The results provide further insight into the role of δ-opioid receptors in the development of sensitization to the stimulant properties of cocaine.

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