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Effects of central neurokinin-1 receptor antagonism on cocaine- and opiate-induced locomotor activity and self-administration behaviour in rats

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Abstract

The neuropeptide substance P (SP) and its preferred receptor, the neurokinin-1 (NK-1) receptor, have been implicated in some of the reward-related behavioural effects of abused drugs, including psychostimulants and opiates. The first objective of the present series of experiments was to assess the role of the NK-1 receptor in two reward-related behavioural effects of cocaine: locomotor activity and self-administration. In tests for locomotor activity, rats were given intracerebroventricular (ICV) infusions of the selective NK-1 receptor antagonist, GR82334 (0, 10, 50 pmol), prior to systemic injections of cocaine. In self-administration experiments, rats were trained to self-administer cocaine on a fixed-ratio 5 (FR5) schedule of reinforcement. Following acquisition of stable responding, animals were pretreated with GR82334 (0, 2, 10, 50 pmol; ICV) prior to subsequent self-administration sessions. Based on evidence suggesting a potentially selective role for NK-1 receptors in opiate reward, we also examined the effects of GR82334 on morphine-induced locomotor activity and heroin self-administration. Results showed that GR82334 had no effect on cocaine-induced locomotor activity or cocaine self-administration, but attenuated morphine-induced locomotor activity and increased heroin self-administration. These findings suggest that endogenous activity at NK-1 receptors may play a specific role in opiate-induced, but not cocaine-induced, locomotor activation and reinforcement.

Keywords: Cocaine; Opiates; Locomotor activity; Self-administration; NK-1 receptors; Substance P; GR82334

1. Introduction

Substance P (SP) is a neuropeptide that has been implicated in reward-related behaviours. Central administration of SP and selective agonists for its preferred receptor, the neurokinin-1 (NK-1) receptor, induce a conditioned place preference (CPP) (Boix et al., 1995; Holzhauer-Oitzl et al., 1987; Nikolaus et al., 1999; Stäubli and Huston, 1985), stimulate locomotor activity (Elliott and Iversen, 1986; Elliott et al., 1992; Naranjo and Del Rio, 1984; Placenza et al., 2004), and induce reinstatement of cocaine-seeking behaviour (Placenza et al., 2004, 2005). These behavioural effects of SP and NK-1 receptor agonists are consistent with evidence showing a facilitatory influence of SP on midbrain dopamine (DA) systems, with its influence on the mesocorticolimbic DA pathway being particularly important in these effects (Cador et al., 1989; Deutch et al., 1985; Elliott et al., 1986a, 1991; Kalivas and Miller, 1984; Overton et al., 1992). Moreover, the effects of SP and NK-1 receptor agonists on CPP, locomotor activity, and reinstatement of cocaine seeking have been shown to be dependent upon DAergic mechanisms, at least in part (Boix et al., 1995; Eison et al., 1982; Elliott et al., 1992; Kelley et al., 1979; Placenza et al., 2004).

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These findings, along with those showing that NK-1 receptors are involved in modulating mesocorticolimbic DA function (Bannon et al., 1983; Elliott et al., 1986b; Hutson et al., 2004; Minabe et al., 1996), suggest that NK-1 receptors may play a role in mediating the behavioural effects of psychostimulants such as cocaine, which exert many of their effects via actions on midbrain DA systems (De Wit and Wise, 1977; Kelly and Iversen, 1976). Evidence implicating NK-1 receptors in cocaine-induced behaviours, however, is mixed. Although in one study it was reported that antagonism of NK-1 receptors blocked the locomotor-activating effects of cocaine (Kraft et al., 2001), in other studies attempts to identify a role for NK-1 receptors in cocaine-induced behaviours have failed. For example, we recently reported that activation of NK-1 receptors reinstated cocaine-seeking behaviour, but that blockade of NK-1 receptors had no effect on reinstatement of cocaine seeking by a priming injection of the drug (Placenza et al., 2005). Consistent with this negative finding, genetic deletion of the NK-1 receptor in mice does not alter the acute locomotor-activating effects of cocaine or the expression of cocaine-induced locomotor sensitization. Similarly, cocaine-induced CPP and cocaine self-administration are unaffected by genetic deletion of the NK-1 receptor (Murtra et al., 2000a; Ripley et al., 2002).

While the reward-related behavioural responses to cocaine are unaltered in mice lacking the NK-1 receptor, these animals do show impairments in their responses to morphine. For example, NK-1 receptor knockout mice do not exhibit morphine-induced locomotor activation, sensitization, place preference conditioning, or self-administration (Murtra et al., 2000a; Ripley et al., 2002). Likewise, selective ablation of NK-1 receptor-expressing neurons in the amygdala abolishes morphine-induced CPP, but has no effect on cocaine-induced CPP (Gadd et al., 2003). These findings suggest that NK-1 receptors play a specific role in the rewarding properties of opiates.

Given the reported inconsistencies in the effects of NK-1 receptor manipulations on cocaine-induced behaviours, an initial objective of the present series of experiments was to further explore and clarify the role of NK-1 receptors in reward-related behaviours induced by cocaine. Specifically, we assessed the effects of intracerebroventricular (ICV) injections of the selective NK-1 receptor antagonist, GR82334, on cocaine-induced locomotor activity and on cocaine self-administration. Given the evidence that NK-1 receptors consistently play a role in the reward-related behavioural effects of opiates, a second objective was to examine the effects of NK-1 receptor blockade on reward-related behaviours induced by opiates. As in the cocaine experiments, the behavioural measures were locomotor activity and drug self-administration. Locomotor activity was induced by morphine, whereas self-administration was maintained by heroin. Heroin, rather than morphine, was used in the self-administration study because we were unsuccessful in our initial attempts to train animals to self-administer morphine.

2. Materials and methods

2.1. Subjects

Male Wistar rats (Charles River, Montreal, QC) weighing 300–350 g were used. Animals were housed individually in Plexiglas cages in a temperature-controlled room maintained on a 12 h light/dark cycle (lights off at 8:30 am). In the locomotor activity experiments, animals had free access to food and water. In the self-administration experiments, animals were maintained on approximately 20 g of lab chow per day. Food restriction was carried out in order to aid in the training of an operant response, and to maintain pre-operative weight and growth rates (Di Ciano and Everitt, 2003). Upon arrival, animals were given a one-week acclimation period prior to any surgical or testing procedures. All procedures were carried out with due regard for the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care, and relevant University of Toronto policy.

2.2. Surgery

Animals were anesthetized with sodium pentobarbital (65 mg/kg; i.p.), immediately following an injection of 0.15 ml of atropine sulfate (0.6 mg/ml; i.p.). Following surgery, each animal received a subcutaneous injection of the analgesic buprenorphine hydrochloride (0.025 mg/kg).

2.2.1. Intravenous catheterization

A chronic indwelling intravenous catheter was implanted into the right jugular vein and anchored with a series of non-absorbable sutures. Catheters were constructed from silastic tubing (Dow Corning Corporation, Midland, MI; 0.51 mm ID × 0.94 mm OD) connected to a threaded guide cannula (Plastics One Inc., Roanoke, VA). The portion of tubing exiting the jugular vein was passed subcutaneously to an opening at the mid-scapular region of the animal's back. The tubing was secured between the skin and fascia with Bard® polypropylene mesh (Davol Inc., Cranston, RI). In order to prevent blocking of the catheter and infection, the opening of the guide cannula was sealed with a plastic cap made from microbore tubing. Catheters were flushed daily with a 0.1 ml solution of saline containing heparin (30 units/ml) and streptokinase (700 units/ml). Catheter patency was verified by injecting 0.1 ml of 20 mg/ml thiopental sodium (Pentothal®) intravenously. If the animal did not become limp within a few seconds of the injection, a new catheter was implanted into the left jugular vein.

2.2.2. Intracranial cannulation

Unilateral guide cannulae (22 gauge) were implanted 1 mm above the left or right lateral ventricle using the following coordinates: −1.0 mm posterior from bregma, +/−1.4 mm from the midline, and −3.4 mm ventral to the skull surface (Paxinos and Watson, 1982). Cannulae were secured to the skull with dental acrylic and jeweller's screws. Dummy guides were placed into the cannulae and

extended 0.1 mm below the tip in order to prevent blockage.

2.3. Drugs

The selective NK-1 receptor antagonist, GR82334 (pGlu-Ala-Pro-Asn-Lys-Phe-Tyr-Pro(spiro-γ-lactam-Leu-Trp-NH_2), was obtained from Sigma-Aldrich Canada Ltd. (Oakville, ON) and dissolved in physiological saline (0.9% NaCl). Heroin hydrochloride was obtained from Almat Pharmachem Inc. (Brampton, ON), and cocaine hydrochloride and morphine sulfate were obtained from BDH Chemicals (Toronto, ON). Each was dissolved in physiological saline.

2.4. Apparatus

2.4.1. Locomotor activity boxes

Locomotor activity testing was conducted using activity-monitoring boxes (34 × 33 × 22.5 cm) constructed in-house. The boxes were constructed of metal and Plexiglas, with wire mesh floors. Locomotor activity was measured via two infrared emitters and corresponding detectors positioned 11 cm apart and 3 cm above the mesh floor. Boxes were interfaced with a computer, using software designed in-house. Two activity measures were recorded: (1) beam breaks and (2) crossovers (defined as a consecutive front and back beam break). All reported activity scores represent number of crossovers.

2.4.2. Self-administration chambers

Self-administration testing was conducted in ventilated and sound-attenuated self-administration chambers measuring 22 cm^3 (Med Associates Inc., Georgia, VT). Each chamber was equipped with two retractable response levers (4.5 cm wide) mounted 7 cm above a steel rod floor. Stimulus lights were positioned 5 cm above each lever. On the opposite wall, there was a houselight centered 2 cm from the top of the chamber. For each chamber, a liquid infusion assembly was connected to an infusion pump located immediately outside of the chamber. At the start of each self-administration session, a houselight was illuminated, the retractable levers were introduced, and the white light above the active lever was illuminated for 20 s. When the active lever was depressed, the infusion pump was activated, delivering a 100 μl infusion. During the infusion, the light located above the active lever was illuminated for 20 s. During this 20 s time-out period, further responses on the active lever were recorded, but did not re-activate the pump. Responding on the inactive lever had no programmed consequences.

2.5. Experimental procedures

2.5.1. ICV microinfusions

GR82334 was injected using a 28 gauge stainless-steel injector extending 1 mm beyond the cannula guide tip and into the ventricle. Using a microinfusion pump, infusions were delivered in a 2 μl volume over a 60 s period. The injector remained in place for an additional 60 s to allow for further drug diffusion.

2.5.2. Locomotor activity testing

Animals were habituated to the activity boxes during two daily 2 h sessions prior to drug testing. On test days, animals were habituated to the activity boxes for 50 min prior to treatment manipulations. Following treatment, animals were immediately returned to the testing apparatus, and locomotor activity was measured for a 2 h period.

2.5.3. Self-administration

Four to six days following surgery, animals were trained to lever press for food pellets under a fixed ratio 1 (FR1) schedule of reinforcement. Rats were allowed a maximum of 100 pellets during 2–3 daily 60 min sessions. Most rats acquired 100 pellets during one of the 60 min sessions on the first day of training, but those that did not were given a second or third day of training.

Following the acquisition of lever pressing for food pellets, animals were trained to self-administer intravenous infusions of cocaine (0.5 mg/kg/infusion) or heroin (0.06 mg/kg/infusion) during daily 2 h sessions. At the start of each session, a 100 μl non-contingent infusion of the self-administered drug was delivered. Animals were initially trained to self-administer on an FR1 schedule of reinforcement. After 5–6 days, an FR5 schedule was implemented in which the FR5 requirement for each infusion began after the 20 s time-out period had expired. Testing began once responding on the FR5 schedule was stable (≤15% variability in the average number of infusions acquired for at least two consecutive days); stable responding was achieved within 7–10 days.

2.6. Effects of ICV infusions of the NK-1 receptor antagonist, GR82334, on cocaine-induced locomotor activity and cocaine self-administration

2.6.1. Cocaine-induced locomotor activity

Animals were tested for locomotor activity as described above. On test days, animals were pretreated with an ICV infusion of GR82334 (0, 10, 50 pmol) 10 min prior to systemic injection of one of two doses of cocaine (10 mg/kg or 20 mg/kg; i.p.; $n=10$ and 12, respectively) or saline (1 ml/kg). Each animal was given all doses of GR82334 in combination with one dose of cocaine (10 or 20 mg/kg) and saline; all within-subjects tests were given in a counterbalanced order and were separated by at least 24 h. The doses of GR82334 were selected on the basis of pilot data showing that in the dose range tested, GR82334 blocks the effects of a selective NK-1 receptor agonist on grooming behaviour and wet dog shakes (unpublished findings).

2.6.2. Cocaine self-administration

Animals ($n=15$) were trained to self-administer cocaine as described above. On test days, animals were pretreated with an ICV infusion of GR82334 (0, 2, 10, 50 pmol) 10 min before the self-administration session. Each animal was given each dose of the antagonist in a counterbalanced order and each test session was separated by at least two consecutive days of stable baseline

responding (≤15% of the average number of infusions for at least 2 consecutive days).

2.7. Effects of ICV infusions of the NK-1 receptor antagonist, GR82334, on morphine-induced locomotor activity and heroin self-administration

2.7.1. Morphine-induced locomotor activity

The procedures used to test the effects of GR82334 on morphine-induced locomotor activity were similar to those described above for cocaine. On test days, animals ($n=10$) were injected systemically with one dose of morphine (5 mg/kg; i.p.) or saline (1 ml/kg), 10 min following pretreatment with GR82334.

2.7.2. Heroin self-administration

Animals ($n=12$) were tested for the effects of GR82334 on heroin self-administration according to the same procedures described above for cocaine self-administration.

2.8. Histology

Upon completion of each experiment, animals were deeply anesthetized with halothane gas and methylene blue dye was injected into the lateral ventricle following the same ICV infusion procedure described above. Animals were then decapitated and the brains removed and stored in formalin (10%) for at least 24 h prior to placement verification. Coronal cuts were made at the level of the lateral ventricles, and the presence of dye in the ventricle was examined.

2.9. Statistical analyses

For locomotor activity experiments, data were analyzed using three-way repeated measures ANOVAs, with Drug condition (cocaine/morphine, saline), Dose of GR82334, and Time as factors. Significant main effects and interactions were further analyzed using Fisher's LSD post-hoc comparisons. Analyses were performed on the data collected throughout the 2 h testing period in 5 min intervals. For self-administration experiments, analyses were performed on the number of cocaine or heroin infusions acquired during the 2 h of testing. Data were analyzed using separate two-way repeated measures ANOVAs, with Hour of testing and Dose of GR82334 as factors. Significant main effects and interactions were further analyzed using Fisher's LSD post-hoc comparisons, as appropriate.

3. Results

3.1. Effects of ICV infusions of GR82334 on cocaine-induced locomotor activity

As shown in Fig. 1, GR82334 had no effect on cocaine-induced locomotor activity at either the 10 mg/kg or 20 mg/kg dose of cocaine. Because the two doses of cocaine were tested in different groups of animals, separate analyses were conducted for each dose group. Three-way repeated measures

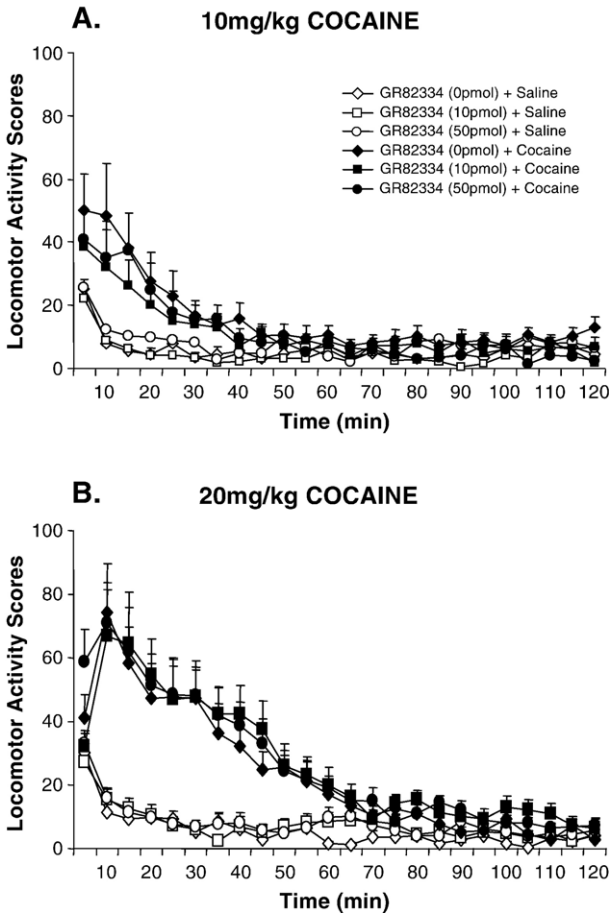

Fig. 1. The effects of ICV administration of GR82334 on cocaine-induced locomotor activity. The graphs depict the mean (±S.E.M.) locomotor activity scores throughout the 2 h post-cocaine (A: 10 mg/kg; i.p. ($n=10$); B: 20 mg/kg; i.p. ($n=12$)) or saline injection period at 5min intervals following ICV infusions of GR82334 (0, 10, 50 pmol).

ANOVAs revealed significant main effects of Drug condition for the 10 mg/kg [$F(1,9)=9.82$, $p<0.01$] and 20 mg/kg [$F(1,11)=45.37$, $p<0.001$] cocaine dose group, and Time for the 10 mg/kg [$F(23,207)=17.22$, $p<0.001$] and 20 mg/kg [$F(23,253)=28.21$, $p<0.001$] dose group, as well as a significant Drug condition by Time interaction for the 10 mg/kg [$F(23,207)=6.81$, $p<0.001$] and 20 mg/kg [$F(23,253)=16.67$, $p<0.001$] dose groups. There were, however, no effects of GR82334 or interactions with GR82334.

3.2. Effects of ICV infusions of GR82334 on cocaine self-administration

It can be seen in Fig. 2 that, consistent with the effects of GR82334 on cocaine-induced locomotor activity, the antagonist had no effect on cocaine self-administration. A two-way repeated measures ANOVA on the number of infusions acquired throughout the 2 h testing period revealed a significant effect of Hour of testing [$F(1,14)=95.04$, $p<0.001$]; animals self-administered more cocaine in the first than second hour of testing. There was, however, no effect of Dose of GR82334 or interaction of Dose of GR82334 by Hour of testing. Responding

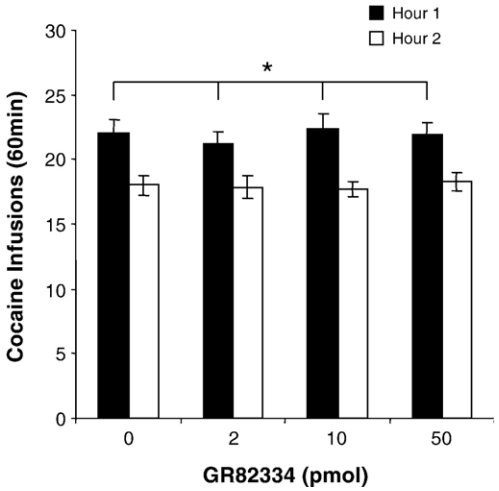

Fig. 2. The effects of ICV administration of GR82334 on cocaine self-administration. The graph depicts the mean (±S.E.M.) number of cocaine infusions acquired during the first and second hour of testing in animals treated with ICV infusions of GR82334 (0, 2, 10, 50 pmol). *Different from Hour 2, $p<0.01$; $n=15$.

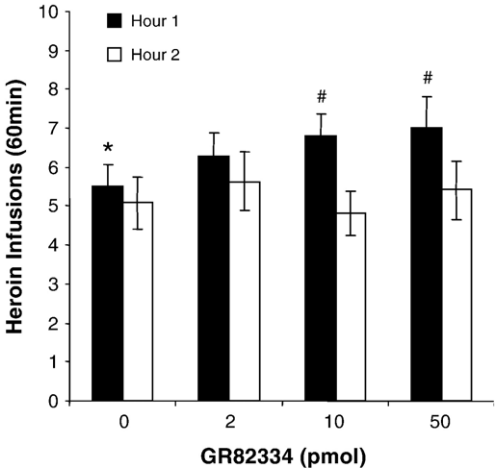

Fig. 4. The effects of ICV administration of GR82334 on heroin self-administration. The graph depicts the mean (±S.E.M.) number of heroin infusions acquired during the first and second hour of testing in animals treated with ICV infusions of GR82334 (0, 2, 10, 50 pmol). *Different from 10 and 50 pmol doses, same hour, $p<0.01$; #Different from Hour 2, same dose, $p<0.01$; $n=12$.

on the inactive lever was found to be very low throughout the experiment and was unaffected by GR82334 (data not shown).

3.3. Effects of ICV infusions of GR82334 on morphine-induced locomotor activity

It can be seen in Fig. 3 that GR82334 significantly attenuated the locomotor-activating effects of morphine throughout most of the first hour of testing. A three-way repeated measures ANOVA revealed a significant main effect of Drug condition [$F(1,9)=9.16$, $p<0.01$], Dose of GR82334 [$F(2,18)=4.56$, $p<0.05$], and Time [$F(23,207)=5.56$, $p<0.001$], as well as a significant Drug condition by Time interaction [$F(23,207)=3.96$, $p<0.001$], and Drug condition by Dose of GR82334 by Time interaction [$F(46,414)=1.44$, $p<0.05$]. Fisher's LSD post-hoc comparisons confirmed that both the 10 and 50 pmol doses of GR82334 significantly attenuated morphine-induced locomotor activity throughout most of the first hour of testing.

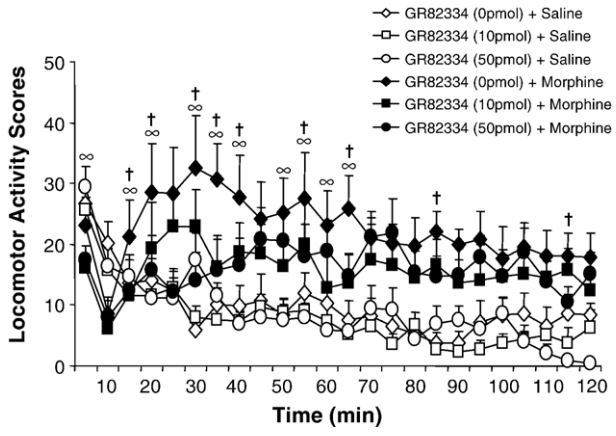

Fig. 3. The effects of ICV administration of GR82334 on morphine-induced locomotor activity. The graph depicts the mean (±S.E.M.) locomotor activity scores throughout the 2 h post-morphine (5 mg/kg; i.p.) or saline injection period at 5 min intervals following ICV infusions of GR82334 (0, 10, 50 pmol). ∞, †Different from GR82334 (10 pmol)+morphine and GR82334 (50 pmol)+morphine, respectively; $p<0.05$; $n=10$.

3.4. Effects of ICV infusions of GR82334 on heroin self-administration

As shown in Fig. 4, GR82334 increased heroin self-administration in a dose-dependent manner. A two-way repeated measures ANOVA on the number of infusions acquired throughout the 2 h testing period revealed a significant effect of Hour of testing [$F(1,11)=50.18$, $p<0.001$], and a significant Dose of GR82334 by Hour of testing interaction [$F(3,33)=3.04$, $p<0.05$]. Fisher's LSD post-hoc comparisons revealed that during the first hour of testing, the 10 and 50 pmol doses of GR82334 significantly increased heroin self-administration ($p<0.005$ for both doses). In addition, at the 10 and 50 pmol doses, animals self-administered more heroin in the first than second hour of testing ($p<0.001$ for both doses). Responding on the inactive lever was found to be very low throughout the experiment and was unaffected by GR82334 (data not shown).

4. Discussion

The first objective of this series of experiments was to further assess a role for NK-1 receptors in reward-related behavioural effects of cocaine. Experimental findings concerning the involvement of NK-1 receptors in the behavioural effects of cocaine are mixed, although the preponderance of evidence suggests a lack of involvement (Gadd et al., 2003; Murtra et al., 2000a; Placenza et al., 2005; Ripley et al., 2002). In this regard, a major finding in the present study was that, across a range of doses, ICV administration of the selective NK-1 receptor antagonist, GR82334, had no effect on cocaine-induced locomotor activation or cocaine self-administration. These findings are consistent with data showing that genetic deletion

of the NK-1 receptor does not impair the reinforcing effects of cocaine (Murtra et al., 2000a; Ripley et al., 2002), that ablation of NK-1 receptors in the amygdala does not block cocaine-induced CPP (Gadd et al., 2003), and that ICV injections of NK-1 receptor antagonists have no effect on the reinstatement of cocaine seeking induced by a priming injection of cocaine (Placenza et al., 2005).

In contrast to the evidence suggesting a lack of involvement of NK-1 receptors in cocaine-induced behaviours, the literature has consistently supported a role for this receptor population in the reward-related behavioural effects of opiates (Gadd et al., 2003; Murtra et al., 2000a; Ripley et al., 2002). The results of the present experiments strengthen and extend this position by demonstrating a modest, but statistically significant, increase in heroin self-administration and attenuation of morphine-induced locomotion following pretreatment with the NK-1 receptor antagonist, GR82334. The fact that GR82334 increased heroin self-administration suggests that the attenuation in morphine-induced locomotor activity is not attributable to a non-specific motor deficit; rather, it is consistent with the idea that NK-1 receptor blockade specifically decreases the positive motivational effects of opiates (Ripley et al., 2002).

Although the present findings do not permit definitive conclusions to be drawn about why blockade of NK-1 receptors increased self-administration of heroin on an FR5 schedule of reinforcement, we would argue that the result most likely reflects a decrease by the antagonist in the reinforcing effects of heroin. Such an interpretation is consistent with the following: (1) previous reports indicating that genetic deletion of the NK-1 receptor abolishes morphine-induced locomotor activity, sensitization, and place preference conditioning, and prevents the acquisition of morphine self-administration in mice (Murtra et al., 2000a; Ripley et al., 2002); (2) our current finding that pharmacological blockade of NK-1 receptors attenuates morphine-induced locomotor activity in rats; and (3) evidence that increases in the rate of drug self-administration on FR schedules of reinforcement are typically indicative of decreases in the reinforcing effects of a drug (Yokel and Wise, 1975, 1976). For example, it has been shown that naloxone or other μ-opioid receptor antagonists dose-dependently increase the rate of heroin self-administration on FR schedules (Negus et al., 1993; Martin et al., 1996; Rocío et al., 1999), in a manner similar to decreasing the unit dose of heroin (Negus et al., 1993; Martin et al., 1996). Indeed, in animals self-administering heroin at the same dose used in the present study (0.06 mg/kg/infusion), and at the same rate (i.e., 5 infusions per hour), naloxone was shown to increase the rate of heroin self-administration (Rocío et al., 1999) to approximately the same magnitude as the NK-1 receptor antagonist (Fig. 4). These findings lend support to our hypothesis that GR82334 increased heroin self-administration by decreasing the reinforcing effects of heroin. Moreover, the present combined effects of the NK-1 receptor antagonist on morphine-induced locomotor activity and heroin self-administration are consistent with the notion that endogenous activity at NK-1 receptors plays a role in the motivational effects of opiates.

In previous studies carried out in mice using genetic deletion or selective lesioning techniques to manipulate the NK-1 receptor, direct comparison between the effects of the NK-1 manipulations on reward-related behavioural effects of cocaine and opiates has consistently supported a role for NK-1 receptors in opiate, but not cocaine, reward (Gadd et al., 2003; Murtra et al., 2000a; Ripley et al., 2002). The present findings are consistent with this argument. Administration of the same doses of an NK-1 receptor antagonist, under similar experimental conditions, altered locomotor activity and drug self-administration maintained by opiates, but not cocaine. Although, in the present study, direct comparison between the effects of the NK-1 manipulations on cocaine- and opiate-induced behaviours is tempting, such comparison must be made with caution. Most notably, we observed considerable differences in baseline response rates between animals self-administering cocaine versus heroin. In particular, at baseline, the rate of cocaine self-administration was approximately 3.5 times that of heroin. It may, therefore, be argued that GR82334 failed to increase cocaine self-administration, as it did heroin self-administration, because animals were already responding at a maximum rate. Though plausible, such an explanation seems unlikely given that there is evidence in the literature that animals are in fact capable of responding for cocaine at a higher rate than what we observed. For example, in animals self-administering cocaine at the same dose (0.5 mg/kg/infusion) and at a similar rate (i.e., 20–25 infusions in the first hour) as our animals, systemic pretreatment with haloperidol has been found to significantly increase cocaine intake on an FR5 schedule of reinforcement, an effect argued to reflect a decrease in the reinforcing effects of cocaine by haloperidol (Higgins et al., 1994). Furthermore, although there were baseline differences in the self-administration rates of cocaine and heroin, it should be noted that, in our locomotor studies, the low challenge dose of cocaine (10 mg/kg) and the challenge dose of morphine induced comparable increases in locomotor activity (see Figs. 1A and 3). Despite these comparable effects on locomotion, the antagonist attenuated morphine-induced locomotor activity only. Thus collectively, our findings are consistent with the view that NK-1 receptor blockade produces impairments in reward-related behaviours maintained or induced by opiates, but not cocaine.

The neurobiological mechanisms mediating the specific modulatory effects of NK-1 receptors on opiate-induced locomotor activation and self-administration are not known. However, one possibility is that blockade of NK-1 receptors interferes with opiate-induced activation of mesocorticolimbic DA neurons, a mechanism through which opiates exert their locomotor-activating and reinforcing effects (Bozarth and Wise, 1981; Gysling and Wang, 1983; Kelley et al., 1980; Shippenberg et al., 1993). SP and the NK-1 receptor play a role in maintaining the activity of mesocorticolimbic DA neurons, both under basal and drug-induced conditions. For example, blockade of NK-1 receptors by systemic injection of an NK-1 receptor antagonist decreased the number of spontaneously active DA neurons in the VTA (Minabe et al., 1996). Similarly, injection of a SP antibody into the NAcc produced increases in concentrations of DA and metabolites, an effect consistent with

intracellular accumulation and metabolism of DA following decreases in DA release (Elliott et al., 1986b). Immunoneutralization of SP in the NAcc also decreased the locomotor-activating effects of amphetamine (Elliott et al., 1986b). These findings suggest that SP not only has a tonic facilitatory influence on mesocorticolimbic DA activity, it may also contribute to the DA-dependent behavioural responses to drugs. Interference with the activity of mesocorticolimbic DA neurons may, therefore, be a mechanism by which blockade of NK-1 receptors attenuates the locomotor-activating and reinforcing effects of opiates.

Although an interaction between NK-1 receptors and DA systems may help to explain the modulatory effects of the NK-1 receptor antagonist on opiate-induced behaviours, it is not immediately apparent how such an interaction would not similarly alter the behavioural effects of cocaine, particularly since DA is also critically involved in the locomotor-activating and reinforcing effects of cocaine (De Wit and Wise, 1977; Kelly and Iversen, 1976). One possibility is that blockade of NK-1 receptors impairs the effects of drugs that stimulate the release of DA, such as opiates or amphetamine, but is not sufficient to overcome the effects of drugs that act exclusively to block DA reuptake, such as cocaine. The finding that NK-1 knockout mice are also insensitive to the reinforcing effects of amphetamine (Murtra et al., 2000b) would support this idea.

In conclusion, the present findings corroborate previous reports that central NK-1 receptors play a role in mediating the reward-related behavioural effects of opiates, but not cocaine, by showing that pharmacological blockade of NK-1 receptors attenuates the locomotor-activating effects of morphine and increases heroin self-administration, but has no effect on cocaine-induced locomotor activity or cocaine self-administration. Thus, the present study provides further support for the role of NK-1 receptors in opiate reinforcement and suggests that the NK-1 receptor may be a promising target for pharmacotherapeutic treatment of opiate addiction.

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