ELSEVIER

European Journal of Pharmacology 358 (1998) 197–202

ejp

Short communication

κ-Opioid receptor blockade with nor-binaltorphimine modulates cocaine self-administration in drug-naive rats

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Received 8 June 1998; revised 26 August 1998; accepted 28 August 1998

Abstract

The modulation of the reinforcing effects of cocaine by the κ-opioid receptor antagonist, nor-binaltorphimine was studied by using the initiation of intravenous self-administration in drug-naive Wistar rats. Treatment with nor-binaltorphimine (3.0 mg/kg s.c.) 48 h before the start of the first of five daily self-administration sessions significantly decreased the intake of cocaine when offered in a threshold unit dose (30 μg per infusion), but had no effect on cocaine intake when it was offered in a higher unit dose (60 μg per infusion). It is concluded that blockade of the κ-opioid receptor by nor-binaltorphimine may produce a rightward shift of the unit dose–response relationship of cocaine reward, thus decreasing the sensitivity to cocaine reward. These data suggest an involvement of endogenous κ-opioid systems in the mechanisms underlying the initiation of cocaine self-administration behaviour.

Keywords: Drug self-administration; Cocaine; Rat; κ-Opioid receptor; Nor-binaltorphimine

1. Introduction

Results from experimental animal studies suggest an involvement of endogenous opioids in the reinforcing effects of the psychostimulant cocaine. That is, treatment with the opioid antagonists naltrexone and naloxone decreases cocaine self-administration behaviour, supposedly by decreasing the reinforcing effects of cocaine (Carroll et al., 1986; De Vry et al., 1989; Corrigall and Coen, 1991; Ramsey and Van Ree, 1991; Kuzmin et al., 1997a; Ramsey et al., 1998). The proposed involvement of endogenous opioid systems in the reinforcing effects of cocaine is also supported by the observation that chronic treatment with naltrexone facilitates the initiation of cocaine self-administration, probably by enhancing its reinforcing effects (Ramsey and Van Ree, 1990). In contrast with these findings, other studies did not find a significant effect of naltrexone on cocaine intake in rats (Ettenberg et al., 1982; Hemby et al., 1996), but these studies involved maintenance conditions of drug self-administration.

The above-mentioned effects on cocaine self-administration were found after blockade with non-selective μ-opioid receptor antagonists, such as naloxone and naltrexone. Recently, the effects of more selective opioids ligands on the reinforcing effects of cocaine were studied in rats. Blockade of the δ-opioid receptor with naltrindole reduced cocaine self-administration in one study (Reid et al., 1995), but failed to affect cocaine intake in another study (De Vries et al., 1995). The involvement of κ-opioid receptors in cocaine reinforcement has been demonstrated. Treatment with the selective κ-opioid receptor agonists, U50,488H (*trans*-3,4-dichloro-*N*-methyl-*N*-(2-1-pyrrolidinyl)-cyclohexyl-benzeacetamide) and spiradoline, decreased cocaine self-administration behaviour (Glick et al., 1995; Kuzmin et al., 1997b). Interestingly, Kuzmin et al. showed that treatment with U50,488H induced self-administration behaviour with lower sub-threshold unit doses of cocaine, doses that did not initiate self-administration under control conditions. In fact, the dose–response curve for cocaine reinforcement was shifted to the left, which could indicate an increased sensitivity for cocaine's reinforcing effects (Kuzmin et al., 1997b). The κ-opioid receptor antagonists nor-binaltorphimine had no effect on cocaine self-administration under maintenance conditions, but fully

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0014-2999/98/$ - see front matter
PII: S0014-2999(98)00637-2

antagonised the effect of U50,488H (Glick et al., 1995). These findings made it of interest to further investigate the involvement of κ-opioid receptors in the reinforcing effects of cocaine during the initiation phase of drug-taking behaviour, particularly since, during this phase the reinforcing effects of drugs are not confounded by other effects of the drug due to chronic exposure. We now examined the effect of the selective κ-opioid receptor antagonist, nor-binaltorphimine, on the reinforcing effects of two unit doses of cocaine using as test the initiation of intravenous cocaine self-administration in rats.

2. Materials and methods

2.1. Animals

The animals were male Wistar rats bred from our own stock (Utrecht, The Netherlands) weighing 180–220 g. Before experiments animals were housed in groups, received food and water ad libitum, and were kept under standard laboratory conditions (i.e., temperature 20–21°C, 60–65% relative humidity and 12 h/12 h light regime with lights on at 7:00 AM). The experimental procedures were approved by the Committee on Animal Experiments of the Faculty of Medicine, Utrecht University.

2.2. Intravenous self-administration

Details of the experimental set-up and procedure have been published previously (see Van Ree et al., 1978; Gerrits et al., 1994). The rats were equipped with a silicone intravenous (i.v.) cannula into the right jugular vein. After surgery each rat was housed individually and was left undisturbed for 4 days, after which their day–night cycle was reversed (lights on between 7:00 PM and 7:00 AM) At this time the food supply was restricted in order to reduce body weights by 20%. Testing started 3 days later. Testing was done in standard operant chambers with two levers protruding from one wall, one of which was marked by a light placed just above the lever. Depression of the lever marked with the light (reinforcement lever) triggered a 13-s i.v. infusion (0.25 ml, fixed-ratio 1). The light went off during the infusion and pressing the lever during this time did not result in an infusion. Depression of the other lever had no programmed consequences (non-reinforcement lever). Drug and lever-press naive animals were allowed to i.v. self-administer a drug solution for 3 h a day or until a maximum of 60 infusions was reached. Testing took place on five consecutive daily sessions. After the fifth and last session, an overdose of Nembutal® was infused through the i.v. cannula to verify proper placement and functioning.

Separate groups of animals were allowed to i.v. self-administer two unit-doses of cocaine (30 (low) or 60 (high) μg per infusion). Animals from each cocaine unit-dose group were treated once, 48 h before the start of the first self-administration session with placebo (saline) or nor-binaltorphimine (3.0 mg kg^{-1}, s.c.). Each rat was tested only once. There were 9 or 10 animals per treatment group.

2.3. Statistical analysis

The results for the number of self-infusions, number of responses on the reinforcement lever and number of responses the non-reinforcement lever obtained on session 2 to 5 were statistically analysed using a two-way analysis of variance with repeated measurements, in which cocaine unit-dose (30 and 60 μg per infusion), treatment (placebo vs. nor-binaltorphimine) and time (four sessions) were the variables. The data of day 1 were not included in the analysis because some rats did not respond regularly over time on that day. Following the overall analysis of the data, separate analyses were performed per cocaine unit-dose.

2.4. Drugs

Nor-binaltorphimine (17,17′-(dicyclopropylmethyl)-6,6′,7,7′-6,6′-imino-7,7′-binorphinan-3,4′,14,14′ tetrol) hydrochloride) (RBI, Natick, MA, USA) was dissolved in warm saline and was administered s.c. in a volume of 1 ml/kg. Cocaine (cocaine-HCl, OPG, Utrecht, The Netherlands) was dissolved in saline and the pH of the drug solution was adjusted to 7.35 ± 0.05. Nembutal® was purchased from Sanofi (Maassluis, The Netherlands).

3. Results

The overall analysis of variance of the number of self-infusions with treatment (nor-binaltorphimine vs. placebo) and cocaine unit doses (30 and 60 μg per infusion) as between-group factors and time (four sessions) as within-subject factor revealed a main time effect with respect to the number of self-infusions over sessions 2–5 (Fig. 1). The interactions treatment × time, dose × time and treatment × dose × time were significant ($F(3,102) = 6.2$, $P < 0.001$; $F(3,102) = 3.5$, $P < 0.02$; $F(3,102) = 3.0$, $P < 0.05$, respectively). The placebo-treated animals showed a significant time effect ($F(3,48) = 22.3$, $P < 0.001$) and no significant dose × time interaction, indicating that in the placebo-treated groups the animals increased their cocaine intake over time similarly in both cocaine unit dose groups.

Subsequently, the numbers of self-infusions per cocaine unit-dose were analysed separately. In the 30 μg per infusion cocaine unit dose group, treatment with nor-binaltorphimine significantly affected the self-infusion rate, as there was and a significant treatment × time interaction ($F(3,51) = 7.0$, $P < 0.001$). In addition, there was a significant time effect ($F(3,51) = 4.6$, $P < 0.01$). In the cocaine

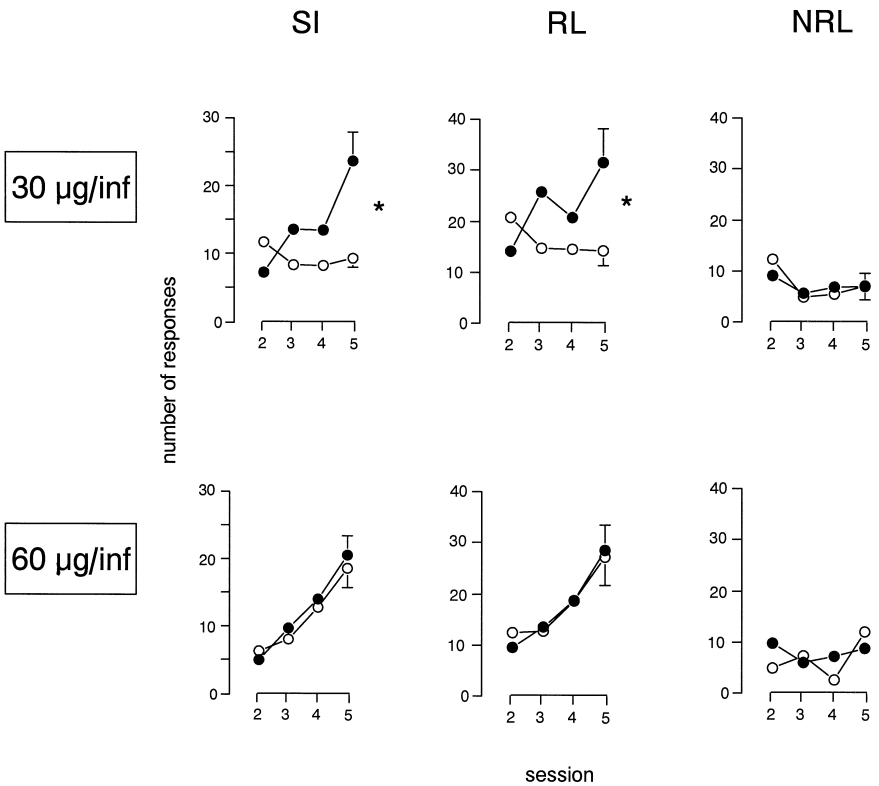

Fig. 1. Effect of nor-binaltorphimine on i.v. self-administration of two doses of cocaine in rats. Animals were treated (s.c.) with placebo (● – ●) or nor-binaltorphimine (3.0 mg/kg) (○ – ○) and were allowed to i.v. cocaine, 30 or 60 μg per infusion. The rats were tested in five consecutive daily 3-h sessions. The mean number of self-infusions (SI) and the number of responses on the reinforcement (RL) and non-reinforcement lever (NRL) (±S.E.M.) are plotted versus the day of testing. *Significant treatment × time effect (see text for details of statistical analyses).

unit dose group of 60 μg per infusion there was significant time effect ($F(3,51) = 29.0$, $P < 0.001$). However, nor-binaltorphimine treatment did not significantly affect self-infusion rate, as neither treatment effect nor interaction treatment × time was significant.

The effect of nor-binaltorphimine on responding on the reinforcement lever, thus including the responses during the time of infusion, closely resembled those on the self-infusion. Overall analysis revealed a significant time effect ($F(3,102) = 8.4$, $P < 0.001$), a significant dose × time and treatment × time interaction effect ($F(3,102) = 3.1$, $P < 0.05$ and $F(3,102) = 3.3$, $P < 0.05$, respectively). Separate analyses of the number of responses on the reinforcement lever per cocaine unit dose revealed a significant treatment × time interaction ($F(3,51) = 3.5$, $P < 0.05$) in the 30 μg per infusion cocaine unit dose group, but not in the higher cocaine unit dose group. A significant time effect ($F(3,51) = 15.6$, $P < 0.001$) was found in the 60 μg per infusion cocaine unit dose group. Two-way analysis of the number of responses on the non-reinforcement lever revealed a no main treatment, dose, time or interaction effect.

The data thus indicate that animals treated with placebo readily self-administer cocaine when it is offered in a unit dose of 30 or 60 μg per infusion. Treatment with nor-binaltorphimine (3.0 mg kg^{-1}, s.c.) significantly blocked cocaine intake in the 30 μg per infusion unit dose group but not in the 60 μg per infusion cocaine unit dose group. Treatment with nor-binaltorphimine caused a rightward shift of the unit dose–response curve for cocaine self-administration, indicating a decreased sensitivity to the reinforcing effects of cocaine. Finally, treatment with nor-binaltorphimine did not significantly affect general locomotor responding as indicated by the lack of effect on the responding on the non-reinforcement lever and a selective blockade of responding on the reinforcement in the 30 μg per infusion cocaine unit dose group only.

4. Discussion

In the present study the effect of treatment with the κ-opioid receptor antagonist, nor-binaltorphimine, on initiation of intravenous (i.v.) self-administration of two unit-doses of cocaine by drug and experimentally naive rats was investigated. Rats treated with placebo and allowed to self-administer the two unit-doses of cocaine, 30 and 60 μg per infusion, had an increased number of self-infusions and of responses on the reinforcement lever over consecutive sessions. Responding on the non-reinforcement lever hardly changed over time. This suggests that the rats

readily initiate cocaine self-administration behaviour and that the behaviour of the rat is directed to obtaining the cocaine infusions. The unit dose of a drug is known to be a major determinant governing its reinforcing efficacy (e.g., Van Ree et al., 1978). An increase in unit dose results in an increased drug intake, and, thus, increased reinforcing efficacy. Accordingly, a decrease in total drug intake indicates a decrease in reinforcing efficacy. During initiation of drug self-administration the relationship between unit dose of the drug and the rate of self-administration (i.e., total number of self-infusions) tends to be an inverted U-shape curve. In the present study the unit dose of 60 μg per infusion was on the descending limb of this curve (total number of self-infusions summed over sessions: 30 μg per infusion, 72.4; 60 μg per infusion, 56.9). Previous studies demonstrated that, under similar experimental conditions, a unit dose of 30 μg cocaine per infusion is a threshold dose, that is the minimum unit dose to initiate properly drug-taking behaviour, and that a higher unit dose of 60 μg per infusion was on the descending limb of the inverted U-shaped unit dose–response curve (De Vry et al., 1989; Kuzmin et al., 1997b). In the present study, treatment with the κ-opioid receptor antagonist, nor-binaltorphimine, significantly decreased cocaine intake in this threshold unit dose group, indicating a decrease in the reinforcing properties of cocaine after blockade of the κ-opioid receptor. κ-Opioid receptor blockade did not affect self-administration behaviour with a higher cocaine unit dose. This finding confirms the effect of treatment with the non-selective opioid receptor antagonist, naltrexone, on self-administration of graded doses of cocaine (De Vry et al., 1989). The effect of the κ-opioid receptor antagonist on cocaine intake is thought to be more or less specific for the reinforcing efficacy of cocaine, as nor-binaltorphimine did not affect responding on the non-reinforcement lever. Responding on this lever has been regarded as an reflection of non-specific behaviour (i.e., motor behaviour). However, non-binaltorphimine did selectively block responding on the reinforcement lever in the threshold cocaine unit dose group only.

To date little is known of the involvement of distinct opioid receptor subtypes in the reinforcing effects of drugs of abuse. There are only few studies showing a possible role of the κ-opioid receptor system in drug self-administration. It is known that treatment with the κ-opioid receptor agonists U50,488H or spiradoline, dose-dependently decreases cocaine and morphine intake in rats during the initiation (Kuzmin et al., 1997b) and maintenance phase (Glick et al., 1995). Treatment with the κ-opioid receptor antagonist nor-binaltorphimine had no effect on heroin (Negus et al., 1997), morphine and cocaine self-administration under maintenance conditions (Glick et al., 1995), but it fully antagonised the effect of U50,488H (Glick et al., 1995). Similar effects of κ-opioid receptor ligands were observed in monkeys self-administering cocaine (Negus et al., 1997). To our knowledge the present data are the first demonstrating an effect of κ-opioid receptor blockade on the initiation of i.v. self-administration of the non-opioid cocaine. Like pure opioid receptor antagonists, mixed opioid receptor agonists–antagonists are able to antagonise the reinforcing effects of cocaine during self-administration. Buprenorphine treatment suppresses cocaine self-administration in rats and mice (Comer et al., 1996; Kuzmin et al., submitted) and in monkeys (Mello et al., 1989, 1990, Winger et al., 1992; Mello et al., 1993; Lukas et al., 1995). Although the exact mechanisms by which buprenorphine reduces cocaine self-administration are unknown, it has been suggested that the μ-agonistic properties of buprenorphine are important for its interaction with cocaine (Mello et al., 1993; Kuzmin et al., submitted). In addition, buprenorphine has κ-antagonistic effects which might contribute to its suppressive effects on cocaine self-administration (Brown et al., 1991). Other mixed receptor opioid agonist–antagonists, such as nalbuphine and butorphanol, decreased the initiation of cocaine self-administration in mice (Kuzmin et al., submitted). When tested against a scale of cocaine unit doses butorphanol produced a rightward shift in the unit dose–response curve for cocaine reward, indicating a decrease of the reinforcing effects of cocaine. Interestingly, co-administration of naloxone did not influence the effects of butorphanol, suggesting an involvement of κ-opioid receptors in this effect. This is consistent with the present finding that κ-opioid blockade with nor-binaltorphimine seems to shift the unit dose–response curve for cocaine reward to the right. Moreover, a recent study it was demonstrated that stimulation of the κ-opioid receptor with U50,488H produced an almost parallel leftward shift of the unit dose–response curves for both cocaine and morphine self-administration (Kuzmin et al., 1997b). Thus, it seems that blockade of the κ-opioid receptors make the animal less sensitive for cocaine reinforcement, while activation of the κ-opioid receptor may result in the opposite.

Hurd and Herkenham (1993) found that levels of dynorphin mRNA and κ-opioid receptor binding in the neostriatum of humans with a history of cocaine dependence were altered. Moreover, cocaine overdose addicts, were found to have an increase in κ_2-opioid receptors in the nucleus accumbens and amygdala (Staley et al., 1997). A number of studies have investigated the effects of cocaine and other psychostimulants on the κ-opioid system in the brain. Subchronic or repeated administration increases striatal levels of dynorphin-immunoreactivity and dynorphin mRNA levels (Peterson and Robertson, 1984; Li et al., 1986, 1988; Hanson et al., 1987, 1988, 1989; Sivam, 1989; Trujillo and Akil, 1989, 1990; Smiley et al., 1990; Trujillo et al., 1990; Gerfen et al., 1991; Hurd et al., 1992; Steiner and Gerfen, 1993; Daunais and McGinty, 1994, 1995; Smith and McGinty, 1994). In addition, increased dynorphin levels were demonstrated in the substantia nigra, nucleus accumbens, but not in the hippocampus (Sivam, 1989; Smiley et al., 1990; Trujillo et al., 1990). With

regard to the density of κ-opioid receptors in the brain it was found that chronic cocaine caused an upregulation in the cingulate cortex, caudate putamen, olfactory tubercle and ventral tegmental area (Unterwald et al., 1994). Although the functional relationship between these alterations and cocaine dependence and administration is not clear, these findings provide evidence for the involvement of κ-opioid systems in cocaine dependence. Experiments on animals self-administering cocaine may shed some more light on the potential involvement of κ-opioid systems in the mechanism of cocaine dependence. Daunais et al. (1993) found an increased expression of dynorphin mRNA in the patch-like areas of the dorsal, but not ventral, striatum. However, because repeated high doses of cocaine were necessary to induce this effect, the authors concluded that the upregulation of the κ-opioid system does not underlie the acute reinforcing effects of cocaine.

The reinforcing properties of cocaine are thought to be primarily mediated through its ability to inhibit presynaptic reuptake of dopamine (Ritz et al., 1987) and thereby increase the concentration of dopamine in the synapse. Moreover, it has been suggested that, in particular, the ventral tegmental–nucleus accumbens (mesolimbic) dopamine pathway is of critical importance for the reinforcing effects of several drugs of abuse (e.g., Willner and Scheel-Krüger, 1991). There is evidence that opioids interfere with the activity of mesolimbic dopamine neurons (e.g., Di Chiara and Imperato, 1988; Spanagel et al., 1992; Devine et al., 1993). As such, modulation of the κ-opioid system might affect the sensitivity of the reinforcing effect of cocaine through a common action on the dopamine activity in the mesolimbic pathway.

To summate, κ-opioid receptor blockade decreased cocaine taking behaviour in rats, and in particular decreased the sensitivity for cocaine reward. Together with the recent finding that stimulation of the κ-opioid receptor caused an increase in the sensitivity for cocaine reward (Kuzmin et al., 1997b), it can thus be suggested that κ-opioid systems play a modulatory role in cocaine self-administration behaviour, especially during the initiation of phase of cocaine dependence.

Acknowledgements

This work was financially supported by Grant no. NWO 47-13-87/47-03-40 from the Dutch Medical Council.

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