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European Journal of Pharmacology 562 (2007) 77–81
www.elsevier.com/locate/ejphar

History of cocaine self-administration alters morphine reinforcement in the rat

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Received 30 October 2006; received in revised form 20 December 2006; accepted 23 January 2007
Available online 8 February 2007

Abstract

It has been shown repeatedly that cocaine pre-exposure may sensitise neurochemical and behavioural responses to opioid drugs. The aim of the present study was to investigate effects of a prior history of cocaine self-administration on morphine reinforcement in the rat. Male Sprague–Dawley rats were allowed to acquire intravenous cocaine self-administration (0.3 mg/kg/infusion) for 20 days. When operant responding for cocaine had stabilised, morphine was introduced instead of cocaine in the next self-administration session. One group of cocaine-exposed rats was allowed to respond for 0.56 mg/kg/infusion of morphine (i.e. the dose which was willingly self-administered by drug-naive controls). The second group was allowed to respond for 0.056 mg/kg/infusion of morphine (i.e. the dose which did not maintain self-administration behaviour in the drug-naive rats). The subjects with the history of cocaine self-administration, in contrast to the drug-naive group, did not maintain operant responding for 0.56 mg/kg/infusion of morphine. These rats easily self-administered the ten times lower dose of the opioid (0.056 mg/kg/infusion). An opioid receptor antagonist, naltrexone (1 mg/kg i.p.) restored the positive reinforcing properties of the higher dose of morphine in the cocaine-exposed rats. Concluding, the present results suggest that prior history of cocaine self-administration sensitises rats to the positive reinforcing properties of morphine.

Keywords: Cocaine; Morphine; Intravenous drug self-administration; Pre-exposure; Reinforcement; Addiction

1. Introduction

It is a common clinical observation that drugs of abuse are used in combinations and that some of these combinations are preferentially co-abused by drug addicts. It is also assumed that pre-exposure to one drug may increase the probability of the use of another drug (Gould et al., 1977; Kozel and Adams, 1986; Robinson and Berridge, 1993). Bearing in mind the concept of the final common pathway of addiction, one may hypothesise that repeated exposure to one drug produces permanent adaptations in the mesolimbic dopaminergic system, which in turn enhance the positive reinforcing properties of another substance (Robinson and Berridge, 1993; Di Chiara, 1995).

It has been shown repeatedly that psychostimulants and opioids are preferentially co-abused by human drug addicts (Kozel and Adams, 1986; Mello and Negus, 1996; Leri et al., 2003). Despite the profound clinical importance of this phenomenon, little is known about its mechanisms. Recently, Ward et al. (2006) have reported that a history of intravenous (i.v.) heroin self-administration led to an upward shift in the cocaine dose–effect curve, suggesting an increase in the positive reinforcing properties of cocaine. Effects of cocaine self-administration on subsequent initiation of opioid self-administration have not been tested as yet. Given the above, we aimed to investigate whether a history of cocaine self-administration might alter the initiation of opioid self-administration. One group of Sprague–Dawley rats was trained to self-administer cocaine (0.3 mg/kg/infusion). When operant responding for cocaine had stabilised, cocaine was replaced by morphine (0.056 or 0.56 mg/kg/infusion) in the next self-administration session. The pattern of morphine self-administration in the cocaine pre-exposed subjects was compared to that found in cocaine-naive controls. The doses of morphine were selected on the basis of our recent experiments. The higher dose of morphine (0.56 mg/kg/infusion) was willingly self-administered by

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0014-2999/$ - see front matter © 2007 Published by Elsevier B.V.
doi:10.1016/j.ejphar.2007.01.064

drug-naive Sprague–Dawley rats. The lower dose (0.056 mg/kg/infusion) did not maintain any self-administration behaviour (Mierzejewski et al., 2003a).

2. Experimental procedures

2.1. Animals

Male Sprague–Dawley rats (Collegium Medicum, Jagiellonian University, Krakow, Poland), weighing approximately 300 g at the start of the experiments, were individually housed in a temperature- and humidity-controlled environment under a 12-h light/dark cycle (lights on at 7:00 p.m.). Food and water were available *ad libitum* in the home cage. Rats were trained and tested between 10:00 a.m. and 5:00 p.m.

Treatment of the rats in the present study was in full accordance with the ethical standards laid down in the respective European (directive no. 86/609/EEC) and Polish regulations. All experimental procedures were reviewed and accepted by the 2nd Animal Care and Use Committee of the Warsaw School of Medicine, Warsaw, Poland.

2.2. Drugs

Cocaine hydrochloride (Pharma Cosmetic, Krakow, Poland) and morphine sulphate (Polfa Kutno S.A., Kutno, Poland) was dissolved in sterile physiological saline (Fresenius Kabi, Warsaw, Poland). Drug concentrations were adjusted daily according to the weight of each rat in order to provide infusions of appropriate dose in a volume of 0.1 ml/rat/infusion over a 2-s period. Naltrexone (Sigma-Aldrich, Poznan, Poland) was dissolved in physiological saline and injected intraperitoneally (i.p.) in a volume of 1 ml/kg.

2.3. Surgery

Silastic catheters were implanted into the right jugular vein under ketamine anaesthesia (100 mg/kg, i.p.; Gedeon Richter, Budapest, Hungary). One week of recovery was allowed before the start of the self-administration procedure. The catheters were flushed each day with a 0.1 ml sterile physiological saline containing heparin (1.25 U/ml; WZF Polfa, Warsaw, Poland) and gentamicin (0.16 mg/kg; Polfa Tarchomin S.A., Warsaw, Poland). The patency of the catheters was tested at the end of the study with thiopental (Sandoz, Basel, Switzerland) for loss of consciousness within 5 s (for details, see Stefanski et al., 1999; Mierzejewski et al., 2003a,b).

2.4. Apparatus

Self-administration sessions were conducted in fourteen standard operant chambers (Coulbourn Instruments, Allentown, PA) equipped with two nose-poke operanda (an "active" and "inactive" hole) and an i.v. injector system (for details, see Stefanski et al., 1999; Mierzejewski et al., 2003a,b). The position of the "active" and "inactive" hole (left vs. right) was counterbalanced across all subjects. The operant chambers were enclosed in ventilated and sound-attenuating cubicles (Coulbourn).

Nose pokes in the "active" holes resulted in delivery of cocaine (0.3 mg/kg/infusion) or morphine (0.056 or 0.56 mg/kg/infusion) whereas nose pokes in the "inactive" holes were recorded but had no programmed consequences. Each nose-poke response produced a brief feedback tone. Following each cocaine (or morphine) infusion there was a 30-s time-out (TO 30 s) period during which responding was recorded but had no programmed consequences. The house light was on during drug availability but was turned off during the entire infusion and time-out period.

Programming of all sessions as well as data recording made use of the WinLinc Coulbourn software and IBM-compatible computers.

2.5. Cocaine and morphine self-administration

2.5.1. Experiment #1

Sixteen rats were randomly assigned to a cocaine-exposed or cocaine-naive group ($n=8$ rats per group). The cocaine-exposed subjects were allowed to acquire cocaine self-administration (0.3 mg/kg/infusion) in 20 consecutive self-administration sessions. The cocaine-naive controls were allowed to acquire morphine self-administration (0.56 mg/kg/infusion) in 40 sessions (for details, see Mierzejewski et al., 2003a,b).

Self-administration sessions were 2 h in duration and there was one session each day, Monday to Friday. At the beginning of each session, one cocaine or morphine injection was automatically delivered to fill the dead space of the catheter. Once responding was initiated, the number of responses required to produce each infusion was gradually increased from FR1 to a final value of FR5 (every fifth response produced drug infusion). The daily 2-h access to cocaine or morphine was continued until the number of responses in the "active" hole stabilised to within 15% for three consecutive days. When responding for cocaine had stabilised, the cocaine-exposed rats were switched from cocaine to morphine (0.56 mg/kg/infusion) in the next self-administration session. These rats were allowed to respond for morphine in 5 consecutive 2-h sessions.

2.5.2. Experiment #2

Sixteen rats were randomly assigned to a cocaine-exposed or cocaine-naive group ($n=8$ rats per group). The cocaine-exposed subjects were allowed to acquire cocaine self-administration (0.3 mg/kg/infusion). The cocaine-naive controls were allowed to acquire morphine self-administration (0.056 mg/kg/infusion). The self-administration procedure was identical to that described above (see Experiment #1).

The doses of morphine for Experiments #1–2 were selected on the basis of our previous experiments. The higher dose of morphine (0.56 mg/kg/infusion) was willingly self-administered by Sprague–Dawley rats. The lower dose (0.056 mg/kg/infusion) did not maintain self-administration behaviour (see Mierzejewski et al., 2003a).

2.5.3. Experiment #3

The rats with the 20-day history of cocaine self-administration, in contrast to the cocaine-naive controls, did not self-administer the higher dose of morphine (0.56 mg/kg/infusion) (Experiment #1). In order to further evaluate this issue, we

decided to check whether an opioid receptor antagonist, naltrexone could restore self-administration of 0.56 mg/kg of morphine in the cocaine-exposed subjects.

Sixteen rats were allowed to acquire cocaine self-administration (0.3 mg/kg/infusion) as described above. When responding for cocaine had stabilised, the rats were randomly assigned to a saline- or naltrexone-treated group ($n=8$ rats per group). Both groups were switched from cocaine to morphine (0.56 mg/kg/infusion) in the next self-administration session. All rats were allowed to respond for morphine in 5 consecutive 2-h sessions. The naltrexone-treated subjects received 1 mg/kg naltrexone (i.p.) 10 min before each morphine self-administration session. The control group received identical volumes of saline.

2.6. Statistical analysis

The STATISTICA software package for Windows (StatSoft, Tulsa, OK, USA) was used to analyse all data. The analysis of variance (ANOVA) with repeated measures on self-administration sessions was used to analyse differences in operant responding between the cocaine-exposed and cocaine-naive rats (Experiments #1–2). Responding for morphine during the last 5 sessions of the maintenance phase in the cocaine-naive controls was compared to responding for morphine in the cocaine-exposed subjects (during the 5 sessions following the switch from cocaine to morphine).

The ANOVA with repeated measures on self-administration session was used to analyse differences between the saline- and naltrexone-treated subjects (Experiment #3). Newman–Keuls test was used for individual *post-hoc* comparisons. Probability (P) levels less than 0.05 were considered significant.

3. Results

In agreement with our previous report (see Mierzejewski et al., 2003a), the acquisition of cocaine and morphine self-administration was different. The drug-naive rats quickly learned cocaine self-administration. A significant difference between nose-poking in the "active" and "inactive" holes was noted in the 5th self-administration session. The acquisition of morphine (0.56 mg/kg/infusion) self-administration was long lasting. A significant difference between nose-poking in the "active" and "inactive" holes was noted in the 25th session. The ten times lower dose of morphine (0.056 mg/kg/infusion) failed to produce self-administration behaviour after 40 consecutive self-administration sessions (Fig. 2A; Mierzejewski et al., 2003a).

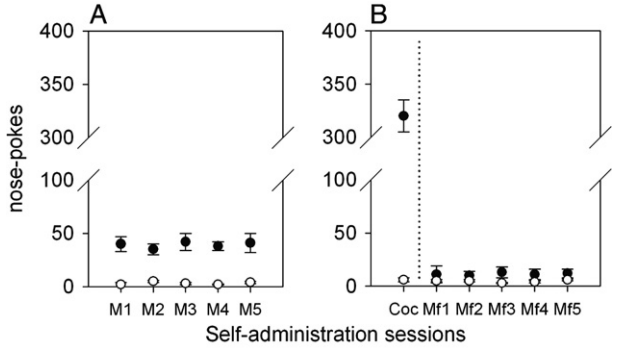

Fig. 1. Morphine (0.56 mg/kg/infusion) self-administration in cocaine-naive rats (A) and in rats with a history of cocaine (0.3 mg/kg/infusion) self-administration (B). Data are presented as the mean (±S.E.M.) number of nose pokes in an "active" (closed circles) and "inactive" hole (open circles) emitted during 2-h self-administration sessions. Panel (A) presents morphine self-administration during the last 5 sessions of a maintenance phase (M1–M5). Panel (B) presents cocaine self-administration behaviour averaged across the last 5 sessions of a maintenance phase (Coc) and morphine self-administration in the 5 sessions following the switch from cocaine to morphine (Mf1–Mf5); $n=8$ rats per group; Coc=cocaine, Mf=morphine.

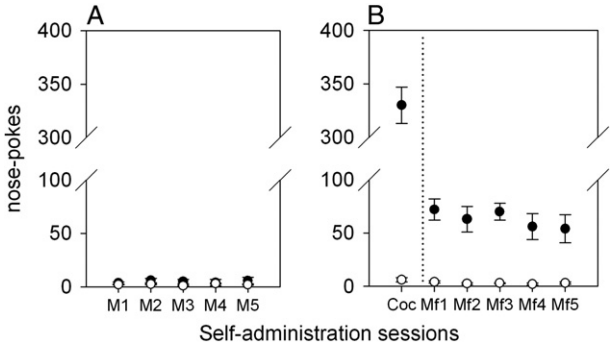

Fig. 2. Morphine (0.056 mg/kg/infusion) self-administration in cocaine-naive rats (A) and in rats with a history of cocaine (0.3 mg/kg/infusion) self-administration (B). Data are presented as the mean (±S.E.M.) number of nose pokes in an "active" (closed circles) and "inactive" hole (open circles) emitted during 2-h self-administration sessions. Panel (A) presents morphine self-administration during the last 5 sessions of a maintenance phase (M1–M5). Panel (B) presents cocaine self-administration behaviour averaged across the last 5 sessions of a maintenance phase (Coc) and morphine self-administration in the 5 sessions following the switch from cocaine to morphine (Mf1–Mf5); $n=8$ rats per group; Coc=cocaine, Mf=morphine.

3.1. Experiment #1

In Experiment #1, we checked whether the history of cocaine self-administration might alter the positive reinforcing properties of the higher dose of morphine (0.56 mg/kg/infusion).

The cocaine-naive group acquired morphine (0.56 mg/kg/infusion) self-administration. The pattern of morphine self-administration was similar to that observed in our recent study (for details, see Mierzejewski et al., 2003a). The ANOVA for the last 5 sessions of the maintenance phase indicated a highly significant Hole effect [$F(1,14)=184.40$, $P<0.0001$; Fig. 1A]. Operant responding for morphine was stable and a Hole × Session interaction was not significant [$F(4,56)=0.34$, $P=0.9$].

In contrast, the subjects with the history of cocaine self-administration did not show operant responding for the higher dose of morphine. The ANOVA indicated a non-significant Hole effect [$F(1,14)=1.90$, $P=0.2$] and a non-significant Hole × Session interaction [$F(4,56)=0.58$, $P=0.64$; Fig. 1B].

3.2. Experiment #2

In Experiment #2, we checked whether the history of cocaine self-administration might alter the positive reinforcing properties of the lower dose of morphine (0.056 mg/kg/infusion).

In agreement with our previous report (Mierzejewski et al., 2003a), the lower dose of morphine was not self-administered by the cocaine-naive group as confirmed by a non-significant Hole effect [$F(1,14)=1.90$, $P=0.2$] and a non-significant Hole × Session interaction [$F(4,56)=1.20$, $P=0.3$; Fig. 2A].

In contrast, the lower dose of morphine maintained self-administration behaviour in the rats with the 20-day history of cocaine self-administration [a Hole effect: $F(1,14)=66.90$, $P<0.001$]. Morphine self-administration remained stable as revealed by a non-significant Hole × Session interaction [$F(4,56)=2.06$, $P>0.05$; Fig. 2B].

The above data might indicate that it was the dose of morphine which determined the difference in morphine reinforcement between the cocaine-naive and cocaine-experienced rats. The lower dose of morphine (0.056 mg/kg/infusion), devoid of any reinforcing properties in the cocaine-naive subjects, was vigorously self-administered by the cocaine-experienced group. The opposite was true for the higher dose of the opioid (0.56 mg/kg/infusion). In order to further evaluate this issue, we compared nose-poking for morphine in Experiments #1–2 with the aid of the four-way ANOVA (Cocaine history × Morphine dose × Hole × Session).

The four-way ANOVA indicated a significant Cocaine history [$F(1,56)=16.40$, $P<0.001$], Morphine dose [1,56)=15.50, $P<0.001$] and Hole effect [$F(1,56)=101.10$, $P<0.001$]. A Session effect was not significant [F4,224)=2.07, $P>0.05$]. A significant Cocaine history × Morphine dose × Hole interaction [$F(1,56)=69.20$, $P<0.001$] reflected the fact that the history of cocaine self-administration suppressed the reinforcing properties of the higher dose but enhanced the reinforcing properties of the lower dose of the opioid.

3.3. Experiment #3

In Experiment #3, we checked whether the partial blockade of μ opioid receptors might restore the positive reinforcing properties of the higher dose of morphine in rats with the history of cocaine-self-administration. Cocaine was replaced with morphine (0.56 mg/kg/infusion) and the rats were randomly assigned to the naltrexone-treated or vehicle-treated group. Naltrexone or its vehicle was injected before each morphine self-administration session.

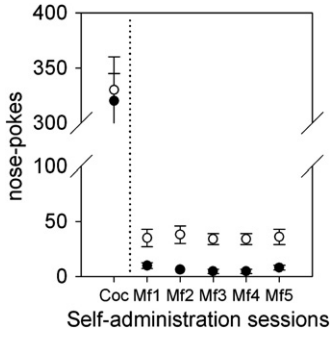

Fig. 3. Effects of an opioid receptor antagonist, naltrexone on morphine (0.56 mg/kg/infusion) self-administration in rats with a history of cocaine self-administration. Naltrexone-treated rats (open symbols) received naltrexone (1 mg/kg, i.p.) 10 min before each morphine self-administration session. A control group (closed symbols) received identical volumes of saline. Data are presented as the mean (±S.E.M.) number of nose pokes in an "active" hole emitted during 2-h self-administration sessions. Coc represents cocaine self-administration behaviour averaged across the last 5 sessions of a maintenance phase. Mf1–Mf5 represents the 5 sessions of morphine self-administration following the switch from cocaine to morphine. For clarity, nose pokes in an "inactive" hole are not shown; $n=8$ rats per group; Coc=cocaine, Mf=morphine.

A significant preference towards the "active" hole was observed in the naltrexone-treated, but not in the vehicle-treated, subjects. This observation was confirmed by the three-way ANOVA (Treatment × Hole × Session) which indicated a significant Treatment effect [$F(1,28)=21.40$, $P<0.001$] and a significant Treatment × Hole interaction [$F(1,28)=22.30$, $P<0.001$]. Other effects and interactions were not significant ($P>0.05$). The number of responses in the "active" hole was significantly higher in the naltrexone-treated group as compared to the vehicle-treated controls across all morphine self-administration sessions (Fig. 3).

4. Discussion

In line with the earlier reports from our laboratory, both cocaine and the higher dose of morphine (0.56 mg/kg/infusion) maintained stable self-administration behaviour in the drug-naive rats (Mierzejewski et al., 2003a,b). Cocaine maintained substantially higher response rates than morphine. As expected, the lower dose of morphine (0.056 mg/kg/infusion) produced no reinforcement in the drug-naive animals (Mierzejewski et al., 2003a).

To the best of our knowledge, this is the first report on effects of prior history of cocaine self-administration on morphine reinforcement in the rat. Our findings indicate a strong effect of cocaine self-administration on morphine-reinforced behaviour. In contrast to the drug-naive animals, the rats with the 20-day history of cocaine self-administration willingly self-administered the lower dose of morphine (0.056 mg/kg) but failed to respond for the higher dose (0.56 mg/kg). Thus, the cocaine-exposed rats demonstrated increased sensitivity to the positive reinforcing effects of 0.056 mg/kg/infusion of morphine while the positive reinforcing properties of the higher dose 'disappeared' after cocaine pre-exposure.

The absence of the reinforcing properties of the higher dose of morphine looks paradoxical in view of the data cited in the Introduction (Nestby et al., 1997; Flores and Stewart, 2000; Ward et al., 2006) and needs some consideration. A typical dose–response curve in the self-administration procedure is characterised by an inverted U shape (Koob, 1992; Stefanski et al., 1999; Mierzejewski et al., 2003a). If cocaine pre-exposure sensitises rats to morphine reinforcement, the whole dose–response curve for morphine self-administration should be shifted to the left, i.e. higher doses should fall on the descending limb of the curve. The results of Experiment #3 seem to confirm the latter assumption. The opioid antagonist, naltrexone restored the positive reinforcing properties of the higher dose of morphine. It has been shown repeatedly that naltrexone shifts opioid dose–response curves to the right and, as a result, blocks self-administration of low doses and enhances responding for high doses of opioid compounds (e.g. Martin et al., 1996; Walker et al., 1999).

Apart from direct interactions with pharmacological effects of morphine, naltrexone could alter operant behaviour through less specific mechanisms related to its aversive stimulus effects. Opioid receptor antagonists produce conditioned place aversion (Vaccarino et al., 1992; Sante et al., 2000) and conditioned taste aversion in rodents (Parker and Rennie, 1992). It has been reported that aversive stimulus (for example stressful or painful stimuli) can affect operant behaviour in the form of disinhibition (Singh and Wickens, 1968) or reinstatement (Goddard and Leri, 2006).

Alternatively, the rapid decrease in operant responding (Fig. 1B) observed in the rats switched from cocaine to the higher dose of morphine may have been secondary to the aversive properties of the opioid. A contrast between expected reward (cocaine) and the new, potentially aversive, stimulus (morphine) could lead to rapid suppression of operant behaviour. This possibility seems to be rather unlikely as a history of cocaine self-administration identical to that used in the present study did not influence morphine-induced conditioned taste aversion and catalepsy (Mierzejewski et al., unpublished observation). Thus, one may assume that, in the present study, cocaine self-administration selectively influenced the positive reinforcing effects of morphine.

There is some evidence indicating that repeated exposures to psychostimulant drugs can enhance the rewarding properties of opioids (and vice versa). It has been reported that pre-exposure to amphetamine increased conditioned place preference induced by morphine. Similarly, morphine pre-exposure enhanced conditioned place preference induced by amphetamine or cocaine (Lett, 1989). In line with the above, Shippenberg et al. (1996) have found that doses of morphine which failed to produce conditioned place preference in drug-naive rats produced marked preferences for a drug-paired compartment in animals which had previously received 5 daily injections of cocaine. Doses of cocaine which did not produce conditioned place preference in drug-naive subjects induced preferences for the drug-paired compartment in animals which had received daily injections of morphine. Interestingly, even a single dose of cocaine (15 mg/kg) enhanced conditioned place preference induced by morphine (Kim et al., 2004). In agreement with the data from the place preference procedure, it has been demonstrated that the 10-day history of heroin self-administration increased cocaine self-administration in the rat (Ward et al., 2006).

In sum, the present results may indicate that prior history of cocaine self-administration enhances the positive reinforcing effects of morphine in the rat. Further studies are needed to determine whether our results generalise to other combinations of psychostimulant and opioid drugs.

Acknowledgement

The study was supported by the Institute of Psychiatry and Neurology (grant no. 65//06 and 67/06).

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