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BRIEF REPORT

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Effects of naltrexone on cocaine- and sucrose-seeking behaviour in response to associated stimuli in rats

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Abstract

The non-selective opioid receptor antagonist naltrexone reduces cocaine-induced reinstatement of drug-seeking behaviour in abstinent rats. The current study sought to determine whether the opioid system is also involved in cocaine-seeking behaviour induced by cocaine-associated stimuli in abstinent rats. Adult male rats were trained to press a lever either to self-administer cocaine or to obtain sucrose pellets in the presence of distinctive discriminative and conditioned stimuli. After a period of extinction, re-exposure to cocaine-associated cues selectively elicited robust and enduring responding at the active lever; sucrose pellet-associated cues revived seeking behaviour less pronouncedly. Pretreatment with naltrexone (0.25, 1, 2.5 mg/kg s.c., 20 min before reinstatement tests) dose dependently prevented cue-induced cocaine-seeking behaviour, whereas (2.5 mg/kg s.c.) did not affect the degree of cue-induced sucrose-seeking behaviour. These results provide the first evidence that naltrexone influences cocaine seeking induced by conditioned stimuli in abstinent rats; this effect appears selective for cocaine reinstatement as opposed to a non-drug reinforcer.

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Introduction

High rates of relapse to drug taking after a long period of abstinence mark experienced cocaine users (Mendelson and Mello, 1996), and are the main obstacle in the long-term treatment of drug abuse. A number of factors contribute to relapse, including re-exposure to the drug itself (Jaffe et al., 1989), exposure to stressors (Sinha et al., 1999) and to stimuli previously associated with drug taking (Childress et al., 1988). Understanding these factors and the underlying neural substrates is crucial for the development of effective anti-relapse treatments.

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Studies in human cocaine addicts suggest the β-endorphin and enkephalin systems are involved in relapse to drug-seeking and drug-taking (Kosten et al., 1989; Zubieta et al., 1996). Although other studies have reported conflicting findings (e.g. see Comer et al., 1993; Modesto-Lowe et al., 1997), encouraging results have been obtained with the non-selective opioid antagonist naltrexone on craving and relapse in human cocaine and/or alcohol users (Kosten et al., 1989; Volpicelli et al., 1992).

At the pre-clinical level opioid antagonists reduced the reinforcing efficacy of cocaine as measured by the threshold for brain stimulation (Bain and Kornestky, 1987), and the rate of cocaine self-administration during acquisition (De Vry et al., 1989) and its maintenance (Corrigall and Coen, 1991; Mello et al., 1990). Studies using the conditioned place preference procedure have indicated the endogenous opioid system is involved in the motivational effects of cocaine (Becker et al., 2002; Rademacher and Steinpreis, 2002).

Repeated treatment with the non-selective μ-opioid receptor antagonist naltrexone reduced cocaine-induced reinstatement of drug-seeking behaviour in rats (Gerrits et al., 2005), and ventral pallidum μ-opioid receptors may be involved in this process (Tang et al., 2005).

Since re-introduction of stimuli associated with drug self-administration plays an important role in the resumption of seeking behaviour that often precedes relapse, the present study assessed the efficacy of acute systemic naltrexone pretreatment in preventing drug-seeking behaviour induced by re-exposure to cocaine-associated cues. To verify whether the effect of naltrexone was selective towards drug-seeking behaviour, rather than a non-specific 'anhedonia' for reward, we also evaluated its efficacy in modulating seeking behaviour for a nutritive reward (sucrose).

Material and methods

Animals

Twenty-four male Sprague–Dawley CD® IGS rats (Charles River, Italy), weighing 225–275 g at the beginning of the experiments were housed individually in a climate-controlled facility with a 12-h light/dark cycle (lights on: 07:30 hours, lights off: 19:30 hours) with food and water ad libitum. All training and experimental sessions were conducted between 09:00 and 18:00 hours and each rat was used only once. All experimental procedures were conducted in conformity with the institutional guidelines that are in compliance with national (D.L. n. 116, G.U., suppl. 40, 18 Febbraio 1992, Circolare No. 8, G.U., 14 Luglio 1994) and international laws and policies (EEC Council Directive 86/609, OJL 358,1, Dec. 12, 1987; Guide for the Care and Use of Laboratory Animals, US National Research Council, 1996).

Drugs

Cocaine hydrochloride (MacFarlan-Smith, Edinburgh, UK) was dissolved in sterile 0.9% saline. Naltrexone hydrochloride (Sigma-Aldrich, Milan, Italy) was dissolved in saline immediately before use and injected subcutaneously (s.c.) in a volume of 1 ml/kg at doses of 0.25, 1 and 2.5 mg/kg 20 min before the reinstatement tests. Doses and pretreatment times were chosen on the basis of previous findings (Burattini et al., 2006; Gerrits et al., 2005).

Apparatus

The self-administration stations consisted of standard rodent operant conditioning chambers (ENV 007, Med Associates, St Albans, VT, USA) enclosed in sound-attenuating, ventilated environmental cubicles. Each chamber was equipped with two retractable levers (one active and one inactive, 12 cm apart, 7 cm above the grid floor) and three lights (2.8 W, 24 V): the house light was positioned in the centre of the ceiling, and the others on the front panel, 4 cm above each lever. Auditory stimuli were presented through a loudspeaker on the back panel. Intravenous (i.v.) infusions were administered by a syringe pump (Med Associates) located inside the sound-attenuating cubicles and connected to a chronic jugular catheter on each rat's back by a connector (C313G, 5UP; Plastic One, VT, USA). The infusion tubing for cocaine was enclosed in a wire coil and screwed into the external mount of the guide cannula. This coil was connected through a swivel apparatus (Med Associates) to the syringe infusion pump. A computer with dedicated software (Med Associates) controlled the input and output to operant cages.

Cocaine self-administration and discrimination training

To facilitate acquisition of operant responding, eight rats were food-restricted (20 g/d) and trained to press a lever for 45-mg food pellets, in 30-min sessions under a fixed ratio 1 schedule (FR1). Once the animals had earned 100 pellets (after 3–4 sessions) they returned to ad-libitum feeding and were surgically prepared with catheter implants.

Catheters were house-made according to Cervo et al. (2003). Briefly, each catheter consisted of silastic tubing (13 cm, Hoechst Marrion Roussel, Milan, Italy) fitted to a guide cannula (C313G, 5UP; Plastic One) which was encased in dental cement (Heraeus Kuler GmbH, Wahrheim, Germany) and anchored to a circular nylon mesh (Small Parts Inc., Miami Lakes, FL, USA). Rats were anaesthetized with equithesin (3 ml/kg i.p.) and the chronic silastic catheter was implanted in the right jugular vein, exiting dorsally between the scapulae.

During post-surgery recovery rats received daily injections of 45 mg/kg s.c. ampicillin (Amplital®, Pharmacia Italia S.p.A., Nerviano, Milan, Italy). Catheter patency was maintained using daily i.v. infusions of heparinized (30 IU/ml) sterile 0.9% saline before and after each self-administration session.

Five days after surgery, rats were trained to press a lever for cocaine reinforcement in daily 2-h sessions under the FR1 schedule, in which pressing the active lever delivered a dose of cocaine (0.25 mg/0.1 ml), infused in 6 s. Cocaine availability was signalled by a white noise 20 dB above the background (S^{D+}), and

each lever press simultaneously activated the infusion pump and the stimulus light above the active lever (CS^+), which remained on during the 20 s time-out (TO) period to prevent accidental overdosing. Starting on day 3, a second, inactive lever was introduced, and the cocaine self-administration sessions were divided into two 1-h sessions. An additional 1-h saline self-administration session was added: saline availability was signalled by the chamber's house light coming on (S^{D-}) and each active-lever press, delivering a saline injection, was paired with a 20-s intermittent tone (7 kHz, 70 dB) (CS^-). This discriminative training regimen was conducted daily for 5 d a week until a stable pattern of responding was reached for cocaine (i.e. the number of drug infusions per session stabilized to within $\pm 10\%$ on three consecutive days) and saline (i.e. <5 lever presses for three consecutive days). Rats were then placed on extinction conditions: 1-h sessions started with extension of both levers, but no discriminative stimuli were presented; each active-lever press activated the syringe pump but neither cocaine or saline, nor the response-contingent cues were delivered. After meeting the extinction criterion (i.e. <5 lever presses for three consecutive sessions), the rats were tested for reinstatement, which consisted of exposing them to the same conditions as in the conditioning phase, except that neither cocaine nor saline was available. In a within-subject design, each rat was tested once with the saline-associated cues and once with each dose of naltrexone or vehicle, and the cocaine-associated stimuli. The five reinstatement sessions were presented according to a Latin square design. Reinstatement sessions were separated by extinction sessions; before being tested for reinstatement each animal had to meet the extinction criterion (Cervo et al., 2003, 2006).

Sucrose pellet-maintained behaviour and discrimination training

To verify whether the effect of naltrexone was specific for cocaine-seeking behaviour, we tested its effect on seeking behaviour induced by re-introduction of sucrose-associated stimuli. Since these cues induce gradually less reinstatement over time (Baptista et al., 2004; Cervo et al., 2006), we used a mixed between within-subjects experimental design. This experiment was conducted under the same conditions as the previous one, except that rats were not catheterized and the reinforcer was a 45-mg sucrose pellet (Noyes formula F, Sandown Scientific, Esher, Surrey, UK).

Two groups of eight rats were trained to press a lever for sucrose pellets with simultaneous presentation of S^Ds predictive of sucrose availability – a white noise 20 dB above the background (S^{D+}) – or non-availability, i.e. the house light on (S^{D-}). Sucrose pellets were available under an FR1 schedule of reinforcement, and active-lever presses were followed by 20-s TO, signalled by the light on above the active lever for sucrose (CS^+), and a 20-s tone for no-reward (CS^-). To avoid satiety each session ended after 30 min or after 30 sucrose pellets had been earned. Extinction and reinstatement test sessions were identical to those for cocaine except that they lasted only 30 min.

After rats reached the extinction criterion (i.e. <5 lever presses for three consecutive sessions), they were tested for reinstatement, after naltrexone (2.5 mg/kg s.c., 20-min pretreatment) or vehicle. Each animal had two test sessions, one with sucrose pellet-associated cues, and one after re-introduction of no-reward-associated stimuli. Reinstatement sessions were separated by three sessions at the extinction criterion. Rats receiving naltrexone during the reinstatement session with the sucrose pellet-associated cues received vehicle with the no-reward-associated stimuli. In the second group of rats the pairing between stimuli and treatment was reversed.

Data analysis

The data are presented as the mean $\pm$ S.E.M. of active- and inactive-lever presses during self-administration, extinction and reinstatement. In each experiment the number of cocaine infusions or sucrose pellets earned in the two separate daily sessions, the last 3 d of saline or no-reward self-administration and the last 3 d of extinction before and between the different reinstatement sessions were analysed separately by one-way analysis of variance (ANOVA) for repeated measurements (cocaine experiment) or mixed factorial ANOVA (sucrose experiment) with sessions as the main factor. Since there was no difference in responding, these values were averaged for further analyses. Thus, the effects of naltrexone on reinstatement induced by cocaine- or sucrose-associated cues were analysed by two-way ANOVA for repeated measurement or mixed factorial ANOVA, respectively, with test session as the main factor. Post-hoc comparisons were done with the Newman–Keuls test.

Results

Effect of naltrexone on seeking behaviour induced by cocaine-associated cues

All animals rapidly acquired cocaine self-administration, reaching the training criterion in 14.5 ± 0.5 d of the discriminative regimen. At the same

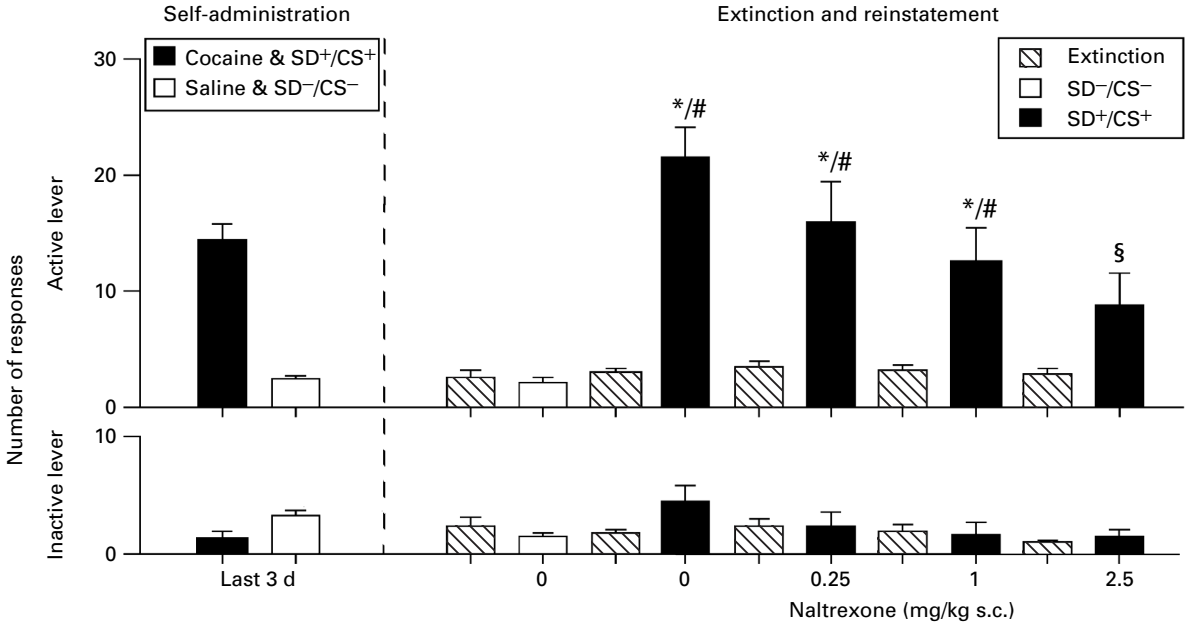

Figure 1. Effects of naltrexone on reinstatement induced by cocaine-associated cues. Histograms represent the mean ($n=8$) ± S.E.M. number of presses on the active and inactive levers. The number of presses during self-administration training (mean of last 3 d), extinction (mean of last 3 d before reinstatement sessions), and in the presence of stimuli associated with no-reward during reinstatement sessions is also shown. Data were analysed by two-way ANOVA for repeated measurements (with test session as the main factor) followed by Newman–Keuls post-hoc comparison. * $p<0.01$ different from the no-reward stimuli, # $p<0.01$ different from the three previous extinction sessions, § $p<0.05$ different from the vehicle + cocaine-associated stimuli group, Newman–Keuls test.

time the number of lever presses during the saline self-administration sessions gradually decreased. Responding at the inactive lever remained low throughout training. During extinction sessions, active-lever pressing gradually decreased and animals reached the extinction criterion in 18 ± 1.2 sessions. Two-way ANOVA for repeated measures found no significant difference in the number of lever presses during the last 3 d of self-administration, no-reward and extinction on either active or inactive levers.

Figure 1 shows the response on the active and inactive levers during self-administration training (mean of the last three sessions), extinction (mean of the last three sessions before reinstatement tests) and reinstatement phase. For comparison, the Figure also shows the mean number of lever presses during the last 3 d of self-administration. Two-way ANOVA for repeated measurement found a significant effect of test sessions [$F(9,140)=13.6$, $p<0.01$] and of levers [$F(1,140)=74.0$, $p<0.01$]. Moreover, a significant interaction between test sessions and levers was also found [$F(9,140)=9.4$, $p<0.01$]. Post-hoc comparisons by Newman–Keuls test revealed that re-introduction of cocaine-associated stimuli in vehicle-pretreated rats significantly increased the number of pressings on the active lever ($p<0.01$ vs. saline-associated cues presentation and vs. the three previous extinction days, Newman–Keuls test) but not on the inactive one ($p>0.05$ vs. saline-associated cues presentation and vs. the three previous extinction days, Newman–Keuls test).

Naltrexone pretreatment significantly modified rats' behaviour after presentation of cocaine-associated stimuli on the active but not on the inactive lever. In fact, post-hoc comparisons by the Newman–Keuls test showed that 1 and 2.5 mg/kg naltrexone significantly reduced the effect of the presentation of cocaine-associated cues ($p<0.05$ vs. vehicle-treated group), which at the highest dose of naltrexone was no longer different from those emitted during the three preceding extinction days ($p>0.05$).

Effect of naltrexone on seeking behaviour induced by sucrose pellet-associated cues

All rats in both groups developed stable lever presses for sucrose pellets, while responding during the no-reward sessions gradually decreased, and the training

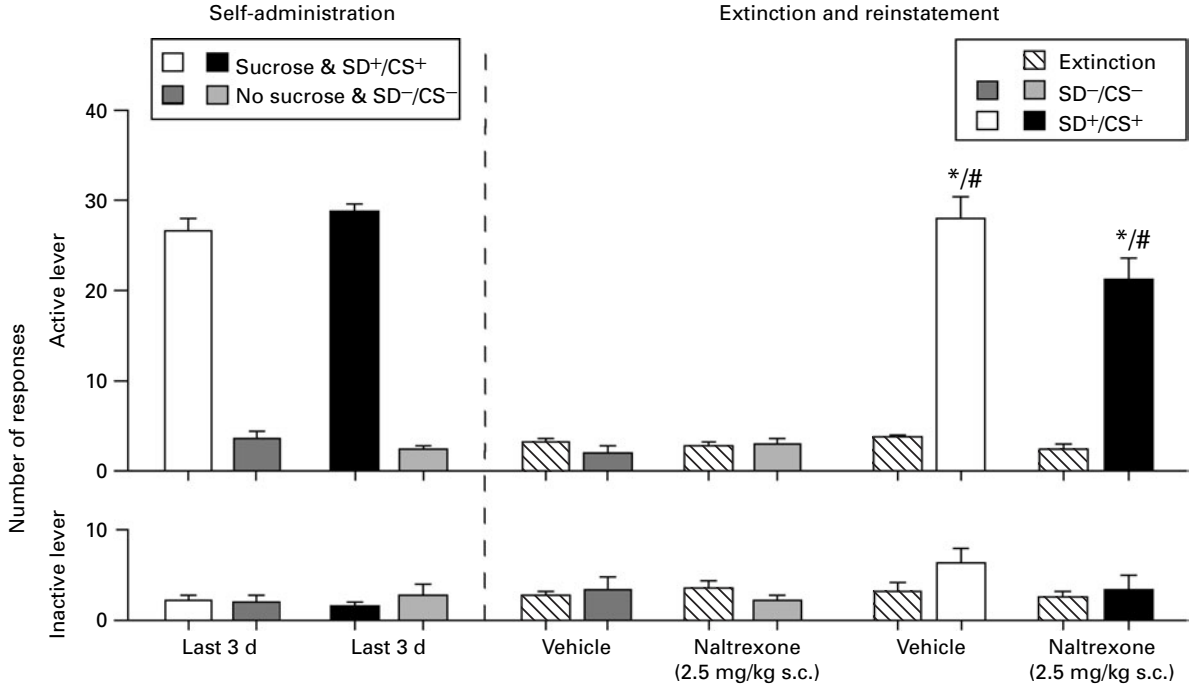

Figure 2. Effects of naltrexone on reinstatement induced by sucrose-associated cues. Results are the mean ± S.E.M. number of presses on the active and inactive levers of two groups of rats ($n = 8$). Reinstatement data were analysed by mixed factorial ANOVA for repeated measurements followed by Newman–Keuls post-hoc comparison (with test session as the main factor). * $p < 0.01$ compared with respective no-sucrose-associated stimuli group, # $p < 0.01$ compared with respective extinction, Newman–Keuls test.

criterion was reached in respectively 25 ± 3.4 and 23.2 ± 1.7 discriminative sessions. No differences in responding by the two groups of animals were observed during the two daily sessions of sucrose pellet self-administration on either active or inactive levers ($p < 0.05$, mixed one-way ANOVA). Likewise, no differences were found in the number of lever presses during the last 3 d of self-administration (mean ± S.E.M. were respectively 25.5 ± 3.8 and 27.8 ± 3.1, and 1.7 ± 1.4 and 2.9 ± 1.8, for the active and inactive levers), no-reward (mean ± S.E.M. 3.3 ± 2.1 and 2.9 ± 1.8, and 2.0 ± 1.4 and 2.5 ± 1.8) in the two groups of animals ($p > 0.05$, mixed one-way ANOVA).

During extinction sessions, active-lever pressing gradually decreased and the two groups of rats reached the extinction criterion in 15.7 ± 4.3 and 17.5 ± 1.6. No differences were observed in the mean of the 3 d preceding the reinstatement test. Mixed factorial ANOVA found a significant effect of sessions [$F(3, 28) = 23.6$, $p < 0.01$] and of levers [$F(3, 9) = 93.8$, $p < 0.01$] as well as an interaction between session × levers [$F(9, 84) = p < 0.01$]. Post-hoc comparisons by Newman–Keuls test revealed that in vehicle-treated animals re-introduction of sucrose-associated cues significantly revived active- ($p < 0.01$) but not inactive- ($p > 0.05$) lever pressing. Naltrexone 2.5 mg/kg did not modify the number of lever presses induced by sucrose-associated cues ($p > 0.05$ compared to vehicle-treated rats and $p < 0.01$ compared to extinction or no-sucrose-associated cues re-introduction). Thus, independently of the treatment, sucrose-associated stimuli revived a significant seeking behaviour ($p < 0.01$ vs. respective extinction and no-sucrose-associated stimuli presentation, Newman–Keuls test). These data are depicted in Figure 2.

Discussion

The main result of the present study is that acute pretreatment with the non-selective opioid receptor antagonist naltrexone attenuates cocaine seeking induced by conditioned stimuli.

Seeking behaviour resumed with both cocaine- and sucrose-associated stimuli, whereas cues not associated with rewards had no such effect. Over the dose range tested (0.25–2.5 mg/kg), naltrexone attenuated

cue-induced cocaine-seeking behaviour, but did not affect the degree of reinstatement to sucrose. This rules out the possibility that naltrexone-induced reduction of lever pressing was due to memory impairment or motor activity abatement, as the animals were still capable of distinguishing the experimental conditions and pressing the lever after naltrexone treatment. It could be argued that differences in the length of reinstatement sessions could account for the different results obtained in the cocaine and the sucrose experiments. This possibility seems unlikely, however, given the pattern of responding during the reinstatement test, which shows the great majority of responses are emitted during the first 30 min of the session, as previously reported (Cervo et al., 2006).

Previous studies have shown that the opioid system is also involved in nutritive behaviour, but to our knowledge these effects have been observed on natural feeding and on food-maintained behaviour. Indeed, seeking behaviour is a distinct process, as demonstrated, for example, by the recent observation that sucrose seeking is decreased by a mGluR 2/3 agonist, which instead has no effect on sucrose self-administration (Bossert et al., 2006). Thus, our interpretation of the selective activity of naltrexone on cocaine seeking induced by conditioned stimuli may support the view that nutritive and non-nutritive reinforcers are processed differentially in the brain, in accordance with previous findings (Carelli et al., 2000). However, it cannot be ruled out that naltrexone preferentially reduces low-level of responding, as in the case of cocaine reinstatement, as opposed to high level behavioural output as in the case of reintroduction of sucrose-associated cues.

The effect of naltrexone indicates that cue-induced reinstatement of cocaine-seeking behaviour is influenced, at least in part, by the endogenous opiate system. Together with recent studies showing that acute pretreatment with naltrexone reduces cue-induced alcohol- (Burattini et al., 2006; Ciccocioppo et al., 2002) and metamphetamine- (Anggadiredja et al., 2004) seeking behaviour, this suggests a more general, common role of opioid receptors in drug-seeking behaviour. Naltrexone is a non-selective opioid antagonist with high affinity for μ, δ and κ receptors, therefore we could not distinguish which receptor was involved in the process. Further studies with more selective agents will address this issue. However, since dopamine levels in the nucleus accumbens (NAc) are increased by discriminative stimuli previously paired with cocaine availability (Weiss et al., 2000), and μ- and δ-opioid receptors influence the activity of mesolimbic dopamine neurons (Devine et al., 1993), one possibility is that naltrexone antagonism at μ- and/or δ-opioid receptors attenuates reinstatement to cocaine-seeking behaviour by preventing a cue-evoked increase of dopamine release in the NAc.

But there are also conflicting observations. Studies of reinstatement induced by a priming injection of cocaine in rats have shown that acute administration of naltrexone fails to suppress cocaine-seeking behaviour (Comer et al., 1993; Gerrits et al., 2005), and that the μ-agonist etonitazine attenuates cocaine-induced reinstatement (Comer et al., 1993). Interestingly, contradictory results have also been obtained for metamphetamine-seeking behaviour. Naltrexone inhibited reinstatement of drug seeking induced by metamphetamine-associated cues, but had no effect on reinstatement induced by drug priming (Anggadiredja et al., 2004). The different effects of naltrexone on cue- and drug-induced reinstatement in both cocaine and metamphetamine experiments might indicate that two distinct neural substrates underlie these processes.

In conclusion, this study provides the first evidence that the endogenous opioid system is involved in the mechanism of cocaine-seeking behaviour induced by cocaine-associated stimuli in abstinent rats. In view of the persistence of motivating effects of drug cues in humans (Childress et al., 1993), further investigation on tolerance to opioid antagonists is advisable. Overall, a better understanding of the interactions between mesolimbic dopamine and opioid systems would greatly enhance our knowledge of the complex mechanisms of addiction, and could lead to improvements in prevention and treatment of relapse.

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Statement of Interest

None.

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