Published in final edited form as:

Synapse. 2013 August ; 67(8): 469–475. doi:10.1002/syn.21653.

The Selective D₃ Receptor Antagonist SB277011A Attenuates Morphine-Triggered Reactivation of Expression of Cocaine-Induced Conditioned Place Preference

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Abstract

We examined the effect of acute administration of the selective D₃ receptor antagonist SB277011A on morphine-triggered reactivation of cocaine-induced conditioned place preference (CPP) in adult male Sprague-Dawley rats. Repeated pairing of animals with 15 mg/kg i.p. of cocaine HCl or vehicle to cue-specific CPP chambers produced a significant CPP response compared to animals paired only with vehicle in both chambers. Expression of the CPP response to cocaine was then extinguished by repeatedly giving the animals vehicle injections in the cocaine-paired chambers. The magnitude of the CPP response after extinction was not significantly different from that of animals paired only with vehicle. Expression of the extinguished CPP response was reactivated by acute administration of 5 mg/kg i.p. of morphine but not by vehicle. Acute administration of 6 or 12 mg/kg i.p. (but not 3 mg/kg) of SB277011A significantly attenuated morphine-triggered reactivation of the cocaine-induced CPP. SB277011A itself (12 mg/kg i.p.) did not reactivate the extinguished CPP response. Overall, SB277011 decreases the incentive motivational actions of morphine. The present findings suggest that central D₃ dopamine receptors are involved in relapse to cocaine-seeking behavior that a final common neural mechanism exists to mediate the incentive motivational effects of psychostimulants and opiates, and that selective dopamine D₃ receptor antagonists constitute promising compounds for treating addiction.

Keywords

dopamine; D3 receptor; cocaine; conditioned place preference

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INTRODUCTION

We examined the effect of acute administration of the selective dopamine D₃ receptor antagonist SB-277011A on morphine-triggered reactivation of cocaine-induced conditioned place preference (CPP) in adult male Sprague-Dawley rats. Repeated pairing of animals with 15 mg/kg i.p. of cocaine HCl or vehicle to cue-specific CPP chambers produced a significant CPP response compared to animals paired only with vehicle in both chambers. Expression of the CPP response to cocaine was then extinguished by repeatedly giving the animals vehicle injections in the cocaine-paired chambers. The magnitude of the CPP response after extinction was not significantly different from that of animals paired only with vehicle. Expression of the extinguished CPP response was reactivated by acute administration of 5 mg/kg i.p. of morphine but not by vehicle. Acute administration of 6 or 12 mg/kg i.p. (but not 3 mg/kg) of SB-277011A significantly attenuated morphine-triggered reactivation of the cocaine-induced CPP. SB-277011A itself (12 mg/kg i.p.) did not reactivate the extinguished CPP response. Overall, SB-277011A decreases the incentive motivational actions of morphine. The present findings suggest that central dopamine D₃ receptors are involved in relapse to cocaine-seeking behavior, that a final common neural mechanism exists to mediate the incentive motivational effects of psychostimulants and opiates, and that selective dopamine D₃ receptor antagonists may constitute promising compounds for treating addiction.

Intense drug craving and relapse to drug-seeking behavior is a distinguishing characteristic of addiction (O'Brien and Gardner, 2006). It is seen in abstinent cocaine and heroin addicts even after many years of withdrawal, when addicts are re-exposed to stress, environmental stimuli previously associated with drug-taking behavior, or the drug itself (de Wit, 1996; Mendelson and Mello, 1996; O'Brien, 1997). Two paradigms have been developed to model relapse at the animal level – the “reinstatement” and “reactivation” models (Gardner and Wise, 2009). In the reinstatement model, animals are allowed to acquire intravenous drug self-administration, then behaviorally extinguished from drug-taking, and then tested for renewed drug-seeking behavior after stress, cue, or drug re-exposure (Shaham and Stewart, 1996; Shaham et al., 1996, 2000, 2002, 2003; Shalev et al., 2002; Bossert et al., 2005; Epstein et al., 2006). In the reactivation model, animals are first allowed to acquire a conditioned place preference (CPP) response to an addictive drug (see below), then behaviorally extinguished from the CPP, and then tested for renewed CPP expression (which is interpreted as drug-seeking behavior) after stress, cue, or drug re-exposure (Mueller and Stewart, 2000; Parker and McDonald, 2000; Manzaneda et al., 2001; Itzhak and Martin, 2002; Mueller et al., 2002; Szumlinski et al., 2002; Ribeiro Do Couto et al., 2003, 2005; Aguilar et al., 2009). It is not improbable that the CPP reactivation model corresponds to contextual cue-induced relapse to drug seeking in humans, although this is based on face validity between the animal model and the human clinical situation.

The CPP animal model is a Pavlovian paradigm in which an unconditioned stimulus (UCS) that produces an appetitive or positive affective state is temporally paired with a specific set of environmental cues which initially constitute a motivationally-neutral set of conditioned stimuli (CS) (Bardo and Bevins, 2000; Tzschenkte, 2007; Aguilar et al., 2009). After

repeated pairing of the UCS and CS, the initially-neutral CS – when presented alone – comes to create (via associative learning) an internal motivational state in the animal similar to that created by the UCS. This can produce an incentive motivational effect that arouses or activates the animal to approach and maintain contact with the environment originally associated with the UCS (Gardner, 2005; Ikemoto, 2010).

The reactivation properties of addictive drug priming or triggering are posited (e.g., Aguilar et al., 2009) to result from the hedonic-activation properties of addictive drugs (Wise, 1980, 1982, 1989, 2008; Gardner, 2005), which produce an incentive motivational state that promotes drug craving and in turn promotes seeking of environmental stimuli previously associated with receipt of drug. Mueller and Stewart (2000) posit that drug administration to animals previously extinguished from a drug-induced CPP serves to “remind” the animal of the significance of the environmental cues previously paired with receipt of drug, and thus to “renew” the incentive motivational value of such cues.

Cross-priming or cross-triggering in animal models of relapse refers to the ability of an addictive drug of one pharmacological class (e.g., an opiate) to trigger or induce reinstatement or reactivation of drug-seeking behavior to an addictive drug of an entirely different pharmacological class (e.g., a psychostimulant). This cross-triggering phenomenon is especially well documented in the reinstatement model of relapse. Morphine reinstates cocaine-seeking (e.g., Stewart, 1984; for review see Shalev et al., 2002), nicotine reinstates ethanol-seeking (Le et al., 2003), 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”) reinstates amphetamine-seeking (Morley et al., 2004), amphetamine reinstates cocaine-seeking (Homberg et al., 2004), heroin reinstates cannabinoid-seeking (Spano et al., 2004), amphetamine (Stewart and Vezina, 1988; De Vries et al., 1998) or cocaine (De Vries et al., 1998) reinstate heroin-seeking.

Cross-triggering of relapse has been also demonstrated with the reactivation model of relapse. Thus, it has been shown that cocaine-seeking is reactivated by methamphetamine (Itzhak and Martin, 2002), methylphenidate (Itzhak and Martin, 2002), morphine (Romieu et al., 2004), phencyclidine (Romieu et al., 2004), nicotine (Romieu et al., 2004), or ethanol (Romieu et al., 2004). Amphetamine reactivates morphine-seeking (Wang et al., 2000).

The phenomenon of cross-triggering or cross-priming of relapse, in both the reinstatement and reactivation models, obviously raises the question of common final neural mechanisms underlying relapse to drug-seeking behavior. Stewart and colleagues (e.g., Stewart, 1984; Stewart and Vezina, 1988; Shaham and Stewart, 1995) were among the first to present evidence that activation of the mesocorticolimbic dopamine system constitutes the final common neural mechanism (see also Shalev et al., 2002; Gardner, 2005, 2011; Gardner and Wise, 2009). This suggestion is supported by experimental findings that dopamine reuptake inhibitors such as GBR12909 (De Vries et al., 1999) and dopamine D₂-like receptor agonists such as bromocriptine (Wise et al., 1990) and quinpirole (Self et al., 1996; De Vries et al., 1999, 2002) trigger relapse to drug-seeking behavior. It is also supported by experimental findings that direct microinjections of amphetamine (Stewart and Vezina, 1988) or dopamine itself (Cornish and Kalivas, 2000) into the dopaminergic axon terminal projection fields of the nucleus accumbens produce relapse to heroin- or cocaine-seeking behavior, and direct

microinjections of morphine into the dopaminergic cell fields of the ventral tegmental area produce relapse to heroin- or cocaine-seeking behavior (Stewart, 1984). It is further supported by experiments using dopamine antagonists, in which it has been consistently found that relapse to cocaine-seeking behavior is attenuated by dopamine D₂-like antagonists (Spealman et al., 1999; Khroyan et al., 2000; Park et al., 2002; Schenk and Gittings, 2003).

Noteworthy, previous studies implicating brain dopaminergic D₂-like receptor mechanisms in relapse to drug-seeking behavior have not used pharmacological tools that satisfactorily distinguish D₂ from D₃ receptor mechanisms. Previously, we have reported that, in rats, acute administration of the selective D₃ receptor antagonist N-[trans-4-[2-(6-Cyano-3,4-dihydro-2(1H)-isoquinoliny)ethyl]cyclohexyl]-4-quinoline carboxamide or SB-277011A significantly attenuates 1) expression of the CPP response to cocaine, heroin, or nicotine and 2) reinstatement of intravenous cocaine self-administration (Heidbreder et al., 2005). Currently, there are no published studies regarding the effect of D₃ receptor antagonists in the CPP reactivation model. Therefore, in this study, we sought to determine: 1) whether morphine cross-triggers relapse to cocaine-seeking behavior in rats using the CPP reactivation model of relapse and 2) whether the acute administration of the highly selective dopamine D₃ receptor antagonist SB-277011A blocks morphine-induced reactivation of the CPP response to cocaine.

MATERIALS AND METHODS

Male Sprague-Dawley rats (Taconic Farms, Germantown, NY), 150-175 g upon arrival, were used for all experiments. The animals were handled and acclimated as previously described (Vorel et al., 2002). The CPP apparatus used was identical to that reported by Vorel et al. (2002). The experimental design and procedure were similar to that of Mueller and Stewart (2000) and consisted of the following 3 phases: 1) initial conditioning; 2) extinction and 3) reactivation. For the conditioning phase, animals were exposed to once-daily pairing sessions. Animals were injected with (-)-cocaine HCl (15 mg/kg i.p. dissolved in a volume of vehicle of 1 ml/kg) or vehicle (1 ml/kg i.p. deionized distilled water) and then immediately confined for 30 min in the appropriate cue-specific chamber. During conditioning, cocaine was paired with one cue-specific environment, and vehicle was paired with the other; cocaine or vehicle exposure (and appropriate environmental pairing) alternated from day to day. One group of animals was paired only with vehicle in both chambers. Animals were subjected to 4 pairing cycles over an 8-day period using a counterbalanced design. Twenty-four hours after the last conditioning, animals were randomly divided into groups of 10 and were individually placed in the CPP apparatus. Subsequently, the animals were allowed to move freely within the apparatus for 15 minutes and the time spent in each chamber was recorded by an automated timer.

Following determination of the initial CPP response to cocaine, animals were given i.p. injections of vehicle in and confined to the chamber originally paired with cocaine for 30 mins every day for 8 consecutive days to behaviorally extinguish the CPP response. The day following the last pairing, animals were placed in the CPP apparatus and the amount of time spent in each chamber was measured for 15 mins.

Twenty-four hours after the last extinction trial, animals (n=10 per group) were given vehicle (1 ml/kg i.p. of 25% w/v solution of 2-hydroxypropyl- β -cyclodextrin) or 3, 6 or 12 mg/kg i.p. of SB-277011A (dissolved in 25% w/v solution of 2-hydroxypropyl- β -cyclodextrin). In addition, the group of animals originally paired with vehicle in both chambers (vehicle-vehicle group) received 12 mg/kg i.p. of SB-277011A. Thirty minutes later, a priming injection of 5 mg/kg i.p. of morphine was administered and animals were immediately placed in the CPP apparatus and the time spent in each chamber was recorded as described above. Morphine sulfate, cocaine HCl and 2-hydroxypropyl- β -cyclodextrin were purchased from Sigma Chemicals (St. Louis, MO). SB-277011A was obtained from the GlaxoSmithKline Psychiatry Center of Excellence for Drug Discovery (Verona, Italy). The dependent variables were the times spent in the cocaine-paired environment versus the vehicle-paired environment. The data were first analyzed using a 2-way (3×6) ANOVA (repeated measurements) with main factors of phase (3 phases: expression, extinction, and reactivation) and treatment (6 groups). Subsequently, a one-way ANOVA was performed with a main factor of drug treatment. Post hoc analyses were conducted using Fisher's least significant difference test.

RESULTS

Data analyses showed a significant phase effect ($F_{2,162} = 81.56$, $p < 0.0001$), treatment effect ($F_{5,162} = 10.19$, $p < 0.0001$), and a significant phase $\times$ treatment interaction ($F_{10,162} = 8.13$, $p < 0.0001$). A subsequent one-way ANOVA of the preferred (drug-paired chamber) side expression data indicated a significant effect of treatment ($F_{5,54} = 8.96$, $p < 0.0001$). Post hoc tests revealed that all groups of animals that received 4 pairings of vehicle and cocaine spent a significantly greater amount of time in the cocaine-paired chamber compared to vehicle-vehicle paired animals (Figure 1A). In contrast, there was no significant difference in the preferred side values for all groups of animals following extinction (one-way ANOVA, $F_{5,54} = 0.16$, $p = 0.976$), i.e. the preferred side values of the vehicle-cocaine animals were decreased after extinction to the same levels as those of vehicle-vehicle paired animals (Figure 1B). Thus, CPP expression was significantly decreased by extinction – vehicle-cocaine CPP during the “expression phase” was decreased to the same levels as vehicle-vehicle CPP in the “extinction phase” in the same animals. Data analyses revealed a significant treatment effect on CPP reactivation (one-way ANOVA, $F_{5,54} = 22.36$, $p < 0.0001$). Administration of 5 mg/kg i.p. of morphine reactivated the cocaine-induced CPP ($p < 0.05$). The morphine-triggered CPP reactivation was significantly attenuated by 6 or 12 mg/kg i.p. (but not 3 mg/kg i.p.) of SB-277011A ($p < 0.05$) – 6 or 12 mg/kg i.p. of SB-277011A decreasing the time spent in the cocaine-paired chamber to the level of vehicle-vehicle paired animals (Figure 1C). Finally, there was no significant difference between the vehicle-vehicle and vehicle-SB-277011A (12 mg/kg i.p.) groups, indicating that SB-277011A does not reactivate CPP expression (Figure 1C).

One of the main findings of the present study is that a non-contingent i.p. injection of 5 mg/kg of morphine can reactivate an extinguished CPP response to cocaine in male rats. This finding is congruent with a report that 5 mg/kg of morphine reactivates an extinguished cocaine-induced CPP in mice (Romieu et al., 2004). Thus, morphine induces *cross*-reactivation in animals that previously expressed a CPP response to cocaine.

DISCUSSION

The present findings also implicate a dopaminergic mechanism underlying such cross-relapse-triggering between addictive drugs, which is congruent with a substantial body of evidence derived from the reinstatement model of relapse (noted above). As much of human drug addiction is *poly*-drug addiction with *cross*-triggering to relapse between different addictive compounds, the present findings suggest that the search for anti-relapse pharmacotherapies should not neglect a focus on dopaminergic brain mechanisms.

This study is the first to report that selective D₃ receptor antagonism attenuates morphine-induced cross-reactivation of an extinguished cocaine-induced CPP. SB-277011A's attenuation of CPP is unlikely to have resulted from either opioid receptor agonist or antagonist action, as SB-277011A is highly selective for dopamine D₃ receptors and does not produce opioid-like behavioral effects (Reavill et al., 2000; Stemp et al., 2000). In addition, in the present study, SB-277011A alone (unlike morphine) did not reactivate the CPP response to cocaine, suggesting that SB-277011A does not have incentive motivational action by itself. This is consistent with previous behavioral studies indicating that, alone, SB-277011A: 1) does not produce a significant CPP response (Vorel et al., 2002); 2) is not self-administered (Xi et al., 2005); and 3) does not produce reinstatement of cocaine self-administration (Xi et al., 2004). It may be argued that SB-277011A's inhibition of morphine-induced reactivation of the CPP response to cocaine is due to an impairment of memory. This is unlikely as the acute administration of SB-277011A does not impair memory in rodents; in fact, it enhances social recognition and prevents scopolamine-induced disruption of spatial memory (Millan et al., 2010).

The present findings that selective D₃ receptor antagonism blocks relapse to cocaine-seeking behavior in the reactivation model is congruent with our previous findings that – in the reinstatement model of relapse – selective D₃ receptor antagonism blocks relapse to drug-seeking behavior triggered by cocaine (Vorel et al., 2002; Xi et al., 2006; Peng et al., 2009), methamphetamine (Higley et al., 2011a), nicotine (Andreoli et al., 2003), stress (Xi et al., 2004), cocaine-associated environmental cues (Gilbert et al., 2005), methamphetamine-associated environmental cues (Higley et al., 2011b), and ethanol plus ethanol-associated environmental cues (Heidbreder et al., 2007) (for reviews, see Heidbreder et al., 2005; Xi and Gardner, 2007, 2008; Gardner, 2008; Heidbreder and Newman, 2010). The present findings are also conceptually congruent with our recent finding that selective dopamine D₃ receptor antagonism reverses the conditioned place *aversion* produced by naloxone-precipitated morphine withdrawal in rats (Rice et al., 2012).

Systemic administration of morphine significantly alters dopaminergic (and non-dopaminergic) neurotransmission (Pierce and Kumaresan, 2006). Dopamine D₃ receptors are located in brain areas that mediate incentive motivation (Diaz et al., 2000; Sokoloff et al., 2006). Thus, it is possible that SB-277011A attenuates the reactivating properties of morphine by blocking dopamine's effects at D₃ receptors. However, this hypothesis remains to be verified on an experimental level.

In conclusion, acute administration of the highly selective dopamine D₃ receptor antagonist SB-277011A significantly attenuates morphine-induced reactivation of an extinguished cocaine-induced CPP in adult male rats. In addition, SB-277011A does not by itself induce CPP reactivation. These results, provided they can be extrapolated to humans, suggest that selective D₃ receptor antagonists could decrease the likelihood of relapse to drug use in human addicts.

Acknowledgments

Contract Grant Sponsor: National Institute of General Medical Sciences (NIGMS) Contract Grant Number: P20GM103499

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Figure 1a

CPP Morphine Reactivation Phase

Figure 1b

Figure 1.

A. The expression of the CPP response to cocaine. Animals received four pairings (1 pairing consists of animals receiving cocaine in one chamber and 24 hrs. later, receiving vehicle in a different chamber) of 15 mg/kg i.p. of cocaine HCl and vehicle, 1 ml/kg i.p. of deionized, distilled water (veh-coc; n=10 per group). In addition, one group of animals (n=10) was paired with vehicle only (veh-veh group). Twenty-four hours after the last pairing (test day), animals were placed in the CPP apparatus and allowed to move freely between the 2 chambers. The amount of time spent in each chamber (drug-paired or non-drug paired) was measured for 15 minutes using an automated device. The values represent the mean time spent in the drug paired chamber $\pm$ the S.E.M. ***Significantly lower than the vehicle-cocaine paired animals, $p < 0.001$ (Two-way ANOVA and Fisher's least significant difference test).

B. The extinction of the expression of the CPP response to cocaine. Twenty-four hours after the CPP expression phase, animals (n=10 per group) were given 1 ml/kg i.p. of deionized, distilled water (vehicle) and placed in the chamber originally paired with cocaine during the expression phase (except for the veh-veh group), once a day for 8 consecutive days. Twenty-four hours after extinction phase, animals were placed in the CPP apparatus and allowed to move freely between the 2 chambers. The amount of time spent in each chamber (drug-paired or non-drug paired) was measured for 15 minutes using an automated device. The values represent the mean time spent in the drug paired chamber $\pm$ the S.E.M.

C. The reactivation of the CPP response to cocaine by morphine (5 mg/kg i.p.). Twenty-four hours after the extinction phase, animals (n=10 per group) were given vehicle (1 ml/kg i.p. of 25% w/v solution of 2-hydroxypropyl- β -cyclodextrin), 3, 6 or 12 mg/kg i.p. of SB-277011A (dissolved in vehicle) and 30 minutes later, animals were given 5 mg/kg i.p. of morphine. The vehicle-vehicle group from the extinction phase received 1 ml/kg i.p. of vehicle and one of the vehicle-cocaine groups received 12 mg/kg i.p. of SB-277011A and 30 minutes later, these animals were given vehicle. Animals were placed immediately in the CPP apparatus and allowed to move freely between the 2 chambers. The amount of time spent in each chamber (drug-paired or non-drug paired) was measured for 15 minutes using an automated device. The values represent the mean time spent in the drug paired chamber $\pm$ the S.E.M. Groups not sharing a common letter are significantly different from each other ($p < 0.001$, two-way ANOVA and Fisher's least significant difference test) except for the sb-mor6 vs. veh-sb12 comparison ($p < 0.05$).