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Dopamine D₃ receptor antagonist SB-277011A inhibits methamphetamine self-administration and methamphetamine-induced reinstatement of drug-seeking in rats

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Abstract

We have previously reported that selective blockade of brain dopamine D₃ receptors by SB-277011A significantly attenuates cocaine self-administration and cocaine-induced reinstatement of drug-seeking behavior. In the present study, we investigated whether SB-277011A similarly inhibits methamphetamine self-administration and methamphetamine-induced reinstatement to drug-seeking behavior. Male Long–Evans rats were allowed to intravenously self-administer methamphetamine (0.05 mg/kg/infusion) under fixed-ratio 2 (FR2) or progressive-ratio (PR) reinforcement conditions, and some rats were tested for methamphetamine-induced reinstatement of drug-seeking behavior after extinction of self-administration. The effects of SB-277011A on each of these methamphetamine-supported behaviors were then tested. Acute intraperitoneal (i.p.) administration of SB-277011A failed to alter methamphetamine self-administration under FR2 reinforcement, but significantly lowered the break-point for methamphetamine self-administration under PR reinforcement. SB-277011A also significantly inhibited methamphetamine-triggered reinstatement of extinguished drug-seeking behavior. Overall, these data show that blockade of dopamine D₃ receptors by SB-277011A attenuates the rewarding and incentive motivational effects of methamphetamine in rats, supporting the development of selective dopamine D₃ antagonists for the treatment of methamphetamine addiction.

Keywords

Methamphetamine; Dopamine D₃ receptor; SB-277011A; Self-administration; Reward; Reinstatement

1. Introduction

Methamphetamine is a widely abused, highly potent and profoundly addictive psychostimulant. It is estimated that more people worldwide use amphetamine-type stimulants than any other illicit drugs besides cannabis (UNODC, World Drug Report, 2010). According to the most recent *National Survey on Drug Use and Health* more than 314,000 Americans over the age of 12 report using methamphetamine in the prior month

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(Substance Abuse and Mental Health Services Administration, 2009). Despite a general decrease in methamphetamine use from the previous survey year, a significant portion of the population continues to use and become dependent on this dangerous drug. Patients with methamphetamine as their primary drug of choice are now the predominant population in public funded treatment systems in most states (Rose and Grant, 2008) with an estimated 3 of every 5 treated patients relapsing during abstinence (Rawson et al., 2006; Rose and Grant, 2008). Currently, there is no approved pharmacotherapy to treat methamphetamine addiction.

Previous research suggests a primary role for the mesolimbic dopamine system in mediating the acute rewarding effects of psychostimulants (Wise, 1996, 2005; Koob and Nestler, 1997; Kalivas and Volkow, 2005; Hyman et al., 2006; Pierce and Kumaresan, 2006). The use of nonselective dopamine receptor agonists and antagonists in the treatment of addiction, however, has been met with very limited clinical success. Since dopamine D₃ receptors are located primarily in the mesolimbic dopamine system, including the ventral tegmental area, nucleus accumbens, islands of Calleja, and olfactory tubercle (Sokoloff et al., 1990), dopamine D₃ receptors have become potential pharmacotherapeutic targets for the treatment of drug addiction (for reviews see, Heidbreder et al., 2005; Le Foll et al., 2005; Newman et al., 2005; Xi and Gardner, 2007; Heidbreder, 2008; Heidbreder and Newman, 2010). Recent studies have shown that pharmacological blockade of the dopamine D₃ receptor with highly selective antagonists such as SB-277011A and NGB2904 blocks both the acquisition and expression of cocaine- and heroin-induced conditioned place preference (Vorel et al., 2002; Ashby et al., 2003), inhibits alcohol intake and reinstatement in ethanol preferring rats (Thanos et al., 2005; Heidbreder et al., 2007), attenuates cocaine-self administration under progressive ratio reinforcement (Xi et al., 2004, 2005, 2006; Gilbert et al., 2005), inhibits cocaine-, cue-, and stress-induced reinstatement to drug seeking (Vorel et al., 2002; Di Ciano et al., 2003; Xi et al., 2004; Gilbert et al., 2005), and inhibits nicotine-, cocaine- and methamphetamine-enhanced brain-stimulation reward in rats (Vorel et al., 2002; Pak et al., 2006; Spiller et al., 2008). However, whether blockade of dopamine D₃ receptors by SB-277011A similarly inhibits methamphetamine-taking and/or methamphetamine-seeking behavior remains unknown.

The purpose of the present study was to investigate the efficacy of SB-277011A on intravenous (i.v.) methamphetamine self-administration, and methamphetamine-induced reinstatement to drug-seeking. SB-277011A is a potent, competitive, dopamine D₃ receptor antagonist with high affinity for human (pK_i = 8.40) and rat (pK_i = 7.97) dopamine D₃ receptors and 120 and 80 fold selectivity for dopamine D₃ versus D₂ receptors in transfected human and rat CHO cells (Reavill et al., 2000). Recent pharmacological MRI studies have shown that SB-277011A readily enters the brain and is localized in dopamine D₃ receptor-rich brain regions such as the nucleus accumbens and islands of Calleja, structures deemed important for drug taking behavior, without significant localization in the caudate putamen, a dopamine D₂ receptor-rich brain region (Schwarz et al., 2004; Choi et al., 2010).

2. Materials and methods

2.1. Subjects

For all experiments, male Long-Evans rats (Charles River Laboratories, Raleigh, NC, USA), experimentally naive and initially weighing 250–300 g, were used. Rats were housed individually on a reversed light-dark cycle (lights on at 1900 h, lights off at 0700 h) climate controlled vivarium with *ad libitum* access to food and water. All experiments were conducted during the animals' dark (active) cycle. Animals were maintained in a facility fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International, and all experimental procedures were conducted in accordance with the

Guide for the Care and Use of Laboratory Animals (National Academy of Sciences, 1996) and were approved by the Animal Care and Use Committee of the National Institute on Drug Abuse of the United States National Institute of Health under the procedures outlined in NIH Policy Manual 3040–2 “Animal Care and Use in the Intramural Program” issued by the NIH Office of the Director – Office of Animal Care and Use.

2.2. Drugs and chemicals

Methamphetamine (Sigma-Aldrich Corporation, St. Louis, MO, USA) was dissolved in sterile physiological saline. SB-277011A was synthesized at MegaPharma Kft. (Budapest, Hungary) and was dissolved in 0.5% Tween-80 (Sigma-RBI, St. Louis, MO, USA) to achieve the 3 drug treatment groups. Tween-80 alone was used as the vehicle.

2.3. General behavioral procedures

2.3.1. Surgery—All animals were prepared for experimentation by surgical catheterization of the right external jugular vein under sodium pentobarbital anesthesia (65 mg/kg, i.p.) using standard aseptic surgical techniques. The right jugular vein was exposed by blunt dissection and the catheter inserted into the vein and sutured into place. The catheter was passed subcutaneously to the skull top and made to exit into a connector (a modified 22-gauge cannula; Plastics One, Roanoke, VA) that was mounted to the skull with jewelers screws and cranioplastic acrylic. The venous catheters were constructed of microrenathane (Braintree Scientific Inc., Braintree, MA, USA). To prevent clogging, catheters were flushed daily with a gentamicin–heparin–saline solution (30 IU/ml heparin; ICN Biochemicals, Cleveland, OH, USA).

2.3.2. Apparatus—All experiments were conducted in standard Med Associates (Georgia, VT, USA) operant response test chambers (32×25×33 cm) housed inside sound-attenuating cubicles filled with a fan for airflow and masking noise. Each test chamber contained 2 retractable levers, (1 active and 1 inactive) located 6.5 cm above the floor, two stimulus cue lights, a speaker for tone delivery, and a house light to provide general illumination. Additionally, each chamber was equipped with a balanced metal arm and spring leash attached to a swivel. Polyethylene tubing extended through the spring leash and was connected to a 10 mL syringe mounted on an infusion pump located outside the sound-attenuating cubicle. Depression of the active lever resulted in activation of the infusion pump; depression of the inactive lever was recorded but had no consequence.

2.3.3. General self-administration procedure—Following recovery from surgery (5–7 days), animals were given the opportunity to self-administer i.v. methamphetamine in daily 3 h sessions. Prior to initiation of the session, the catheter for each rat was connected to a microprocessor-controlled syringe pump by polyethylene tubing, which was fed through a liquid swivel that allowed freedom of movement. Training sessions began with the insertion of the retractable operant lever into the chamber and illumination of a 15-watt house-light that remained on for the duration of the session. Each depression of the active lever produced delivery of i.v. methamphetamine (0.05 mg/kg/infusion) in a volume of 0.08 ml delivered over 4.6 s. A white cue light located above the lever was illuminated, and a cue tone (~20 dB above background) was emitted for the duration of the infusion. A fixed-ratio 1 (FR1) schedule of reinforcement was used for 3 to 5 days to facilitate acquisition of self-administration behavior. After this initial training, animals were switched to FR2 reinforcement, such that two lever presses resulted in one i.v. infusion of methamphetamine. The dose of methamphetamine was chosen based on pilot data indicating that rats trained with 0.05 mg/kg/infusion display rapid and reliable acquisition of self-administration (Higley et al., 2011). To avoid overdose each animal was limited to a maximum of 50 methamphetamine infusions per 3 h session. This dose of methamphetamine is within the

range of the descending limb of the methamphetamine dose–response self administration curve in rats and is appropriate to measure reliable and stable dose-dependent effects (Kitamura et al., 2006; Wee et al., 2007).

2.4. Effect of SB-277011A on FR2 methamphetamine self-administration

Rats (N = 12) continued self-administration for i.v. methamphetamine under FR2 reinforcement until the following criteria for stable responding were met: 1) less than 10% variability in the mean interresponse interval; 2) less than 10% variability in number of infusions; and 3) less than 10% variability in number of active lever presses for a minimum of 3 consecutive days. After stable rates of responding were established (7–10 days), each subject randomly received one of four treatment doses of SB-277011A (0, 6, 12, 24 mg/kg, i.p.) 30 min prior to the test session; all other conditions were the same. Prior to testing the next dose of SB-277011A, all animals underwent a 5- to 7-day period of FR2 methamphetamine self-administration until a stable baseline was re-established. This schedule was maintained until each animal received each treatment dose. The order of treatment was counterbalanced.

2.5. Effect of SB-277011A on progressive ratio breakpoint for methamphetamine self-administration

Self-administration training was identical to that outlined above. Following stable FR2 responding for methamphetamine, all rats (N = 48) were switched to a progressive ratio (PR) schedule of reinforcement. The PR reinforcement model imposes incrementally increasing work demand upon the animal to receive a single reinforcer. In this experiment, the number of lever presses required to receive a single infusion of methamphetamine was increased according to the following series: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, and 603 and ended when the rat failed to achieve a response within 1 h (Richardson and Roberts, 1996). The break-point is defined as the final completed response requirement and is considered an index of the strength of the reinforcer. Animals continued with daily PR self-administration sessions until they achieved stability and day-to-day variability in break point ratios were within 1–2 ratio increments for three consecutive days. Once stable, animals were randomly divided into one of four groups (n = 12 each) based on their subsequent treatment dose of SB-277011A. On the test day, SB-277011A (0, 6, 12, or 24 mg/kg) was administered 30 min prior to initiation of PR self-administration and break-point values were measured.

2.6. Effect of SB-277011A on methamphetamine-induced reinstatement of drug-seeking behavior

Self administration training was identical to that outlined above in Section 2.4. After stable FR2 responding for i.v. methamphetamine was established (approximately 14 days), rats underwent 2 weeks of daily extinction trials, during which methamphetamine was replaced by saline, and the methamphetamine-associated cue light and tone were turned off. Thus, active lever presses led only to a saline infusion. Daily 3-hour extinction sessions continued for each animal until the animal made less than 10 lever presses per 3-hour session for at least three consecutive days. After meeting this extinction criterion, animals were divided into four groups of 8–10 rats each for reinstatement testing.

On the reinstatement test day, rats received one of four treatment doses of SB-277011A (0, 6, 12, or 24 mg/kg, i.p.) 30 min prior to the initiation of the 3-hour reinstatement test. The drug-induced reinstatement test was initiated by a single priming injection of methamphetamine (1 mg/kg, i.p.). This dose has been found to produce robust reinstatement of methamphetamine seeking in previous studies (Rogers et al., 2008; Schwendt et al., 2009). The reinstatement test conditions were identical to those in the extinction sessions.

Active lever presses (reinstatement) were recorded but did not lead to methamphetamine infusions or presentation of the conditioned cue-light and tone. The reinstatement test session lasted 3 h.

2.7. Data analyses

All data are presented as means ($\pm$ S.E.M.). One-way analysis of variance (ANOVA) was used to analyze the effect of SB-277011A on methamphetamine self-administration and methamphetamine-induced reinstatement to drug seeking. Individual group comparisons were carried out using pre-planned Bonferroni t-tests. The minimal acceptable statistical significance was set at a probability level of $P < 0.05$ for all tests.

3. Results

3.1. SB-277011A has no effect on methamphetamine self-administration under FR2 reinforcement

SB-277011A administered 30 min prior to self-administration sessions for i.v. methamphetamine had no statistically significant effect on self-administration behavior (see Fig. 1). A one-way ANOVA for repeated measures over the SB-277011A dose range revealed no statistically significant effect of SB-277011A on methamphetamine self-administration under FR2 reinforcement conditions ($F_{3,39} = 0.56$; $P = \text{NS}$, $n = 12$, Fig. 1A). Regardless of treatment condition, rats earned an average of 50 methamphetamine infusions (the maximum allowed). Additionally, Fig. 1B shows that there was no statistically significant effect of SB-277011A on the number of inactive lever presses ($F_{3,39} = 0.44$; $P = \text{NS}$, $n = 12$).

3.2. SB-277011A inhibits methamphetamine self-administration under PR reinforcement

Fig. 2A shows a representative record of an individual animal's active lever pressing pattern for i.v. methamphetamine under a PR schedule following pretreatment with vehicle and 12 mg/kg SB-277011A. Each vertical line indicates a methamphetamine infusion (0.05 mg/kg per infusion). The number between the vertical lines indicates the number of lever presses (PR ratio) required for a subsequent methamphetamine infusion with the last number indicating the PR break-point. Fig. 2A shows reduction in PR Breakpoint from 178 after pretreatment with vehicle (0.5% Tween80, i.p.; upper trace) to a break-point of 50 following pretreatment with SB-277011A (12 mg/kg i.p., lower trace). Considering all test groups (rather than a single illustrative animal), treatment with SB-277011A significantly lowered the break-point for methamphetamine self-administration reinforced under a PR schedule. Fig. 2B illustrates the group data for the observed SB-277011A decrease in PR break-point. A one-way ANOVA revealed a statistically significant treatment main effect ($F_{3,44} = 28.27$, $P < 0.001$, $2 = 0.71$). Individual group comparisons using the Bonferroni test revealed a significant reduction in break-point after 12 mg/kg ($t = 7.31$, $P < 0.001$, $n = 12$) or 24 mg/kg ($t = 7.14$, $P < 0.001$, $n = 12$) SB-277011A when compared to the vehicle treated group. There were no statistically significant differences between pretreatment with 12 or 24 mg/kg SB-277011A.

3.3. SB-277011A inhibits methamphetamine-induced reinstatement to drug-seeking behavior

Fig. 3A illustrates the total number of active lever presses observed during the last session of methamphetamine self-administration, the last session of extinction, and the reinstatement test session in the four different SB-277011A dose groups. A single, non-contingent methamphetamine priming dose (1 mg/kg, i.p.) produced robust reinstatement of extinguished operant responding (i.e., active lever presses) in rats previously reinforced by i.v. methamphetamine infusions. One-way ANOVA revealed a statistically significant

overall main effect of SB-277011A on methamphetamine-triggered reinstatement ($F_{3, 44} = 47.47$, $P < 0.001$). Bonferroni individual group comparisons indicate a significant reduction in active lever presses during reinstatement testing following pretreatment with 12 mg/kg SB-277011A ($t = 5.52$, $P < 0.001$, $n = 12$) or 24mg/kg SB-277011A ($t = 5.84$, $P < 0.001$, $n = 12$), but not after 6mg/kg SB-277011A ($t = 1.60$, $P = \text{NS}$), when compared with the vehicle pretreatment. Fig. 3B illustrates the total number of inactive lever presses observed during the last session of methamphetamine self-administration, the last session of extinction, and the reinstatement test session in the four different treatment groups, indicating that SB-277011A had no effect on inactive lever presses during reinstatement testing ($F_{3, 44} = 1.70$, $P = \text{NS}$). There were also no statistically significant differences in inactive lever presses during the last session of methamphetamine self-administration ($F_{3, 44} = 1.52$, $P = \text{NS}$) or the last session of extinction ($F_{3, 44} = 0.14$, $P = \text{NS}$) among the four SB-277011A dose groups.

4. Discussion

The present study demonstrates that pretreatment with SB-277011A significantly inhibits methamphetamine self-administration maintained under PR reinforcement conditions and methamphetamine-induced reinstatement of drug-seeking behavior, suggesting antagonism by SB-277011A of methamphetamine's rewarding effects and relapse potential. Our results suggest a role for dopamine D_3 receptors in reducing excessive methamphetamine intake associated with compulsive psychostimulant use in the later stages of the methamphetamine addiction process and support further studies of SB-277011A or other dopamine D_3 receptor antagonists as a treatment modality for methamphetamine addiction.

Intravenous drug self-administration is the most commonly used animal model to evaluate a drug's rewarding effects (Gardner, 2000). There are several self-administration paradigms, including FR and PR self-administration. Under FR reinforcement, the addictive drug is readily available to animals under low-effort (low work demand) and high-payoff (high unit dose of drug) conditions. In the present study, we found that SB-277011A had no effect on methamphetamine self-administration under low-effort, high reward conditions (FR2) but reduced methamphetamine break points under the high-effort, low reward payoff condition demanded by the PR schedule of reinforcement. Since the PR breakpoint is drug dose- or reward strength-dependent, it has been considered a measure of rewarding efficacy (Roberts, 1989; Roberts et al., 1989; Richardson and Roberts, 1996). The present finding that SB-277011A decreases PR break-point for methamphetamine self-administration suggests a reduction in methamphetamine reward and/or motivation for methamphetamine-seeking behavior. This is congruent with previous reports that selective dopamine D_3 antagonists inhibit cocaine, alcohol, and nicotine self-administration under PR or high FR conditions, but not under lower FR conditions (Pilla et al., 1999; Vorel et al., 2002; Di Ciano et al., 2003; Gal and Gyertyan, 2003; Gilbert et al., 2005; Xi et al., 2005, 2006) and provide further support that dopamine D_3 receptors may be implicated in the motivation to self-administer drugs under schedules with high response requirements and strongly modulate the influence of environmental stimuli on drug seeking behavior (Vorel et al., 2002; Xi et al., 2004, 2005, 2006; Le Foll et al., 2005; Xi and Gardner, 2007; Heidbreder, 2008; Higley et al., 2011; Orio et al., 2010).

There are several possible explanations for SB-277011A's inhibition of methamphetamine self-administration under PR but not low FR reinforcement conditions. First, FR2 reinforcement demands less work to obtain much higher cumulative methamphetamine. In the present study, the total methamphetamine intake during FR2 methamphetamine self-administration averaged 2.5 mg methamphetamine, considerably higher than the average total intake of 0.80 mg methamphetamine during PR self-administration. The greater brain

concentration of methamphetamine achieved in the FR2 schedule may counteract the efficacy of dopamine D₃ antagonism by SB-277011A. Another possibility is the relative insensitivity of low FR reinforcement schedules to changes in reward efficacy (Roberts, 1989; Roberts et al., 1989; Arnold and Roberts, 1997; Gardner, 2000).

Drug craving and relapse to illicit drug use is a core feature of drug addiction (Mendelson and Mello, 1996; O'Brien, 1997). In humans, relapse to drug use can be triggered by adventitious drug administration, exposure to environmental stimuli previously associated with drug use, or stress (Jaffe et al., 1989; O'Brien et al., 1992; Sinha, 2001). In experimental animals, relapse to drug use can be similarly modeled with the reinstatement paradigm triggered by addictive drugs, drug-associated cues or stress (Shaham and Stewart, 1994; Shalev et al., 2000; Stewart, 2000; Shalev, 2003). The present study demonstrated that methamphetamine priming reliably and rapidly reinstated extinguished drug-seeking behavior in rats with previous methamphetamine self-administration history. It is important to note that the animals responded primarily and preferentially on the active lever, the lever previously associated with methamphetamine infusions, confirming that the elicited response resulted from prior conditioning and demonstrating drug-seeking behavior rather than a general increase in arousal. Thus, SB-277011A's action appears specific to drug-induced reinstatement rather than nonspecific behavioral disruption, as the number of inactive lever presses was unaffected by treatment with SB-277011A. These findings are consistent with previous literature (Self et al., 1996; Khroyan et al., 2000; Cervo et al., 2003) and suggest a potential role for dopamine D₃ receptor antagonism in attenuating drug craving and relapse in humans.

In summary, the present study demonstrates that blockade of dopamine D₃ receptors by SB-277011A significantly and dose-dependently inhibits methamphetamine-taking and methamphetamine-seeking behavior in rats, providing additional evidence supporting an important role of dopamine D₃ receptors in psychostimulant abuse and addiction. It also provides a rationale for continued medication development of selective dopamine D₃ antagonists as pharmacotherapeutic compounds for the treatment of psychostimulant addiction. Further studies will be necessary to explore the effects of chronic dopamine D₃ receptor antagonist administration on methamphetamine (or other drug)-taking and/or drug-seeking behavior in experimental animals.

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Fig. 1.

Effect of SB-277011A (0, 6, 12, 24 mg/kg, i.p.) on methamphetamine self-administration under fixed-ratio 2 (FR2) reinforcement schedules in rats. Panel A shows that there was no significant effect of SB-277011A on the number of methamphetamine infusions. Panel B shows there was no effect of SB-277011A on inactive lever presses.

Fig. 2.

Effect of SB-277011A (0, 6, 12, 24 mg/kg, i.p.) on methamphetamine self-administration under a progressive ratio (PR) schedule of reinforcement. Panel A shows representative individual responding for methamphetamine (0.05 mg/kg/infusion) after vehicle (upper trace) or 12 mg/kg SB-277011A (lower trace) pretreatment. Panel B shows a significant reduction in PR breakpoint following pretreatment with SB-277011A. Data are presented as percent change from baseline. *** $P < 0.001$, when compared with the vehicle treatment group.

Fig. 3. Effect of SB-277011A (0, 6, 12, 24 mg/kg, i.p.) on reinstatement of drug-induced drug-seeking behavior triggered by a single priming dose of methamphetamine (1 mg/kg, i.p.). Panel A shows a statistically significant reduction in methamphetamine-induced reinstatement after 12 and 24 but not 6 mg/kg SB-277011A when compared with the vehicle treatment group. Panel B shows that SB-277011A had no effect on inactive lever presses. ** $P < 0.001$, when compared with the vehicle treatment group.