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The Selective Dopamine D₃ Receptor Antagonist SB-277011A Significantly Accelerates Extinction to Environmental Cues Associated with Cocaine-Induced Place Preference in Male Sprague-Dawley Rats

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The re-exposure of rodents (Shaham et al., 2003), as well as human addicts (Epstein et al., 2006), to environmental cues associated with various drugs of abuse produces or elicits drug-seeking behavior. Extinction has been used to reduce conditioned responses to drugs in humans and animals. Extinction is an active learning process, where repetitive presentations of conditioned stimuli (CS) (e.g. environmental cues) in the absence of the unconditioned stimulus (UCS) (e.g. addictive drug or appetitive stimuli) previously paired with the CS weakens the magnitude or frequency of response to the CS (Myers and Carlezon, 2010). Treatments or behavioral modifications that reduce the time required for extinction could be useful in decreasing cue-induced drug seeking behavior in human addicts. In rats, acute administration of the highly selective dopamine D₃ receptor antagonist SB-277011A (Heidbreder et al., 2005) significantly attenuates the expression of conditioned place preference (CPP) to cocaine, heroin and nicotine (Heidbreder and Newman, 2010). In this study, we determined whether i.p. administration of SB-277011A facilitates extinction of cocaine-induced CPP in rats.

Naïve, male Sprague-Dawley rats (190–210 grams at the start of CPP pairings, Taconic Farms, Germantown, NY) were used in all experiments. Animals were housed, maintained, fed, and watered as previously described (Ashby et al., 2015). The conditioning and testing of all animals was carried out between 1100 and 1800 h. An automated, two-chambered, Plexiglas CPP apparatus was used as previously described (Ashby et al., 2015), with modifications. All animals were acclimated, transported to the laboratory, handled and given

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CPP pairings with cocaine (15 mg/kg i.p.) or vehicle (1 mL/kg of deionized distilled water) as previously described (Ashby et al., 2015). Animals in each group were randomly assigned to a 2×2 factorial design – the factors being the pairing chamber and the order of pairing. On the CPP test day (day 0), animals (n=40) were randomly divided into four groups of 10 and the CPP response was measured as previously described (Ashby et al., 2015).

Following establishment of the initial CPP response (day 0) to cocaine, animals underwent extinction. Thirty minutes before placement in CPP chambers, animals were paired with either vehicle or SB-277011A (1 mL/kg i.p. of 25% w/v of 2-hydroxypropyl- β -cyclodextrin (HPBCD)) or 3, 6 or 12 mg/kg i.p. of SB-277011A (dissolved in 25% w/v of HPBCD) and confined to the appropriate chamber for 30 min every day for 8 consecutive days (extinction days 1–8). The amount of time spent in each chamber was automatically measured for 15 min.

(-)-Cocaine HCl was purchased from Sigma-Aldrich (St. Louis, MO) and HPBCD was purchased from Tocris Bioscience (Division of Bio-Techne, Minneapolis, MN). SB-277011A was obtained from GlaxoSmithKline (Harlow, Essex, U.K.). All drug doses are expressed as the salt weight.

All data are expressed as mean $\pm$ standard error of the mean. The data were analyzed using a 2-way ANOVA (repeated measurements) with main factors of days and SB-277011A dose. Post hoc analyses were conducted using Fisher's least significant difference test.

Statistical analysis indicated a significant effect of days ($F(8, 288) = 98.9, p < 0.0001$), drug treatment ($F(3, 36) = 45.2, p < 0.0001$), and days $\times$ drug treatment ($F(24, 288) = 3.6, p < 0.0001$) on the time animals spent in the cocaine-paired chamber of the CPP apparatus. Subsequent post hoc analyses indicated that there were no significant differences amongst SB-277011A dose groups in CPP response measured on the CPP test day (day 0, Figure 1). SB-277011A, at 3 mg/kg, significantly facilitated extinction on Days 2, 3, 4 and 5 ($p = 0.0002, p < 0.0001, p < 0.0001$ and $p = 0.0097$, respectively) compared to vehicle-treated animals (Figure 1). The 6 and 12 mg/kg doses of SB-277011A significantly facilitated extinction on Days 1-5 ($p < 0.0001$) and the magnitude of the CPP response on Day 6 was significantly decreased ($p = 0.01$) by 6 mg/kg of SB-277011A (Fig. 1) compared to vehicle-treated animals. The effect of 6 mg/kg of SB-277011A was greater than that of 3 mg/kg on Day 1 ($p = 0.0001$). The 12 mg/kg dose of SB-277011A produced a significantly greater decrease in the CPP response compared to 3 mg/kg of SB-277011A on Days 1, 2 and 3 ($p < 0.0001, p = 0.0027$ and $p = 0.04$, respectively). There was no significant difference between 6 and 12 mg/kg SB-277011A in decreasing the CPP response on Days 1-8.

Thus, acute i.p. administration of SB-277011A significantly accelerated extinction to cocaine-induced CPP. It is unlikely that SB-277011A's action is due to an impairment of memory as acute administration of SB-277011A in rodents enhances social memory recognition and attenuates scopolamine-induced memory impairment (Millan et al., 2007). Furthermore, at the doses used in this study, acute injections of SB-277011A do not produce adverse psychomotor effects in rats (Heidbreder et al., 2005). The facilitation of extinction

by SB-277011A is not due to aversive actions because at doses used in this study, SB-277011A does not produce aversion (Vorel et al., 2002).

Congruent with present findings, Song et al. (2014) reported that in an operant paradigm, the selective D₃ receptor antagonist YQA-14 (12.5 and 25 mg/kg) significantly facilitated extinction (decrease in active lever presses) from cocaine seeking behavior in adult male Long Evans rats. Drug-associated cues or stimuli, which can maintain extinction, increase DA release in certain mesolimbic brain areas (Aragona et al., 2009; Carelli et al., 2003) that contain dopamine D₃ receptors (Heidbreder et al., 2005). Thus, D₃ receptor antagonism by SB-277011A could explain why it facilitates extinction of cocaine-induced CPP. If these results can be translated to humans, they suggest that highly selective D₃ antagonists may be used to facilitate extinction and decrease the likelihood of cue-induced relapse to cocaine use.

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Fig.1.

Effect of SB-277011A on extinction of cocaine-induced CPP. Day 0 represents the CPP test day following 4 CPP pairings with vehicle and cocaine. During extinction testing, animals were given vehicle, 3, 6, or 12 mg/kg i.p. of SB-277011A 30 min before placement in the CPP apparatus and the CPP response was measured for 15 min. Ten animals were used for each group. Each value represents the mean number of minutes $\pm$ S.E.M. SB = SB-277011A; Veh = Vehicle (1 mL/kg of 25% w/v of 2-hydroxypropyl- β -cyclodextrin * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$; # = $P < 0.0001$