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Effect of a D3 receptor antagonist on context-induced reinstatement of nicotine seeking

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ABSTRACT

Despite the existence of several treatment options for smoking cessation, the rate of relapse after treatment is very high. We and others have proposed that targeting the dopamine D3 receptor (DRD3) may be a good strategy for treatment of nicotine dependence. In human participants, reintroduction to an environment previously associated with drug-taking may induce relapse. In animals, such phenomenon can be studied using the context-induced reinstatement paradigm. As the role of DRD3 in context-induced reinstatement of nicotine-seeking has not yet been explored, we investigated the effects of different doses of the selective DRD3 antagonist SB-277011-A on this reinstatement. Sprague–Dawley adult rats were first trained to self-administer nicotine and subsequently underwent extinction in a second context for 5–7 days. We evaluated the effect of 1, 3 or 10 mg/kg of SB-277011-A administered prior to the reintroduction to the training context. We used two different designs: 1) a between-subjects design with a unique reinstatement test; and 2) a counterbalanced within-subjects design, with 4 reinstatement tests. Our findings indicate that, in the within-subjects design, the magnitude of responding induced by the context-induced reinstatement of nicotine seeking was robust during the first reinstatement test, but significantly decreased with repeated testing. SB-277011-A (10 mg/kg) blocked context-induced reinstatement of nicotine-seeking at first exposure to the context (between-subjects design), but not after repeated context exposure which produced weaker reinstatement over days. Our results support a role for DRD3 mediating context-induced reinstatement of nicotine seeking, but these effects may not be sustained over time. Further studies should explore this in human participants for validation.

1. Introduction

Dopamine is substantially involved in addiction, therefore it has been investigated for the treatment of drug dependence (Le Foll et al., 2009). The dopamine D3 receptor (DRD3) is located in limbic areas, suggesting a good target for the development of pharmacological treatments for drug addiction (Heidbreder et al., 2005; Le Foll et al., 2003, 2005a, 2005b, 2014; Newman et al., 2005). Supporting this hypothesis, several studies have shown that DRD3 ligands were effective at decreasing the reinstatement of drug-seeking (Achat-Mendes et al., 2010; Andreoli et al., 2003; Cervo et al., 2005; Gal and Gyertyan, 2006; Gilbert et al., 2005; Heidbreder et al., 2007; Higley et al., 2011; Khaled et al., 2010; Spiller et al., 2008; Vorel et al., 2002) suggesting that these ligands may be useful as pharmacological treatments in preventing relapse to drugs.

Conditioned stimuli (CSs) present in the environment where drug is taken form associations with drug use, contributing to the ability of drugs to induce relapse (de Wit and Stewart, 1981; Stewart et al., 1984). According to this view, because the association is formed between the environment and drug use during training, the context acquires excitatory conditioned stimulus (CS+) properties. As extinction occurs in a different scenario, the training contexts retain their motivational properties and induce reinstatement of drug-seeking.

Reinstatement models are animal models that simulate the ability of environmental stimuli and drugs to induce relapse to drug-seeking (de Wit and Stewart, 1981, 1983; Gerber and Stretch, 1975; Stretch and Gerber, 1973). Relapse is of clear importance to the study of addiction, and reinstatement is an animal model with high predictive validity (Epstein et al., 2006) that has been studied in rodents and humans (Chiamulera et al., 1996; McKee, 2009; Shaham et al., 1997) and

Abbreviations: DRD3, Dopamine D3 receptor; DRD2, Dopamine D2 receptor; CSs, conditioned stimuli; CS+, excitatory conditioned stimulus; FR, fixed ratio; ANOVA, Analysis of Variance; SEM, Standard Error of the Mean.

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might be very helpful to explore novel treatment approaches for drug addiction. The context-induced reinstatement of drug seeking seems to be a good animal model to investigate nicotine-seeking behaviour (Diergaarde et al., 2008; Wing and Shoaib, 2008). This model was first developed by Crombag and Shaham (2002), and it consists of training animals to self-administer drugs in one context (context A). Once self-administration is stable, the lever responding leading to a drug infusion is extinguished in a different context (context B). Differences between contexts mostly include visual, tactile and auditory features. The reinstatement of drug-seeking is assessed by reintroducing the animal to context A (the original drug-paired context), when the active lever pressing does not lead to the drug infusion (Bossert and Stern, 2014; Bossert et al., 2012; Crombag and Shaham, 2002; Crombag et al., 2002; Fuchs et al., 2007). This model simulates the situation when an individual is trying to quit and is suddenly exposed to a previous environment where the individual smoked.

Previous studies of context-induced reinstatement have been valuable in determining some of the neurobiology underlying this type of responding. They have identified that the mesocorticolimbic dopamine system is involved in context-induced reinstatements for cocaine (Fuchs et al., 2007) and heroin (Bossert et al., 2007; Crombag et al., 2008; Marchant et al., 2014). The DRD3 has been shown to be involved in the mechanism of relapse since DRD3 antagonists decreased reinstatement of drug-seeking for various drugs of abuse (Cervo et al., 2005, 2007; Di Ciano et al., 2003; Gal and Gyertyan, 2006; Gilbert et al., 2005; Higley et al., 2011), including nicotine (Andreoli et al., 2003; Khaled et al., 2010). Despite the findings supporting the involvement of DRD3 in different animal models of relapse, there are no investigations into the role of DRD3 antagonists on context-induced reinstatement of nicotine seeking.

This study sought to investigate the effects of different doses of the DRD3 antagonist SB-277011-A on context-induced reinstatement of nicotine-seeking in rats. Two different designs were used, one between-subjects and one within-subjects, the latter having 4 repeated reinstatement tests. The repeated exposure to the context during reinstatement has validity as it represents the most common situation occurred during quitting, when an individual suddenly encounters a place where they once smoked.

2. Material and methods

2.1. Subjects

A total of 33 Sprague–Dawley rats weighing 300–340 g at the time of surgery (Charles River, QC, Canada) were individually housed under a reversed 12 h light/dark cycle (lights on at 7 pm). Rats were maintained on a diet of approximately 16 g (4 food pellets) of lab chow per day throughout the experiment. Water was freely available, and food was given in the afternoon always after the daily sessions. Experiments were performed between 9 am and 1 pm, 5 or 6 days a week. Experimental procedures were carried out in compliance with the guidelines of the Canadian Council on Animal Care, and were approved by the Centre for Addiction and Mental Health Institutional Animal Care Committee.

2.2. Drugs

Nicotine hydrogen tartrate (Sigma-Aldrich, St Louis, MO, USA) was dissolved in saline and pH adjusted to 7.3–7.4. Nicotine (0.03 mg/kg/infusion) was administered intravenously in a volume of 0.1 ml/kg/infusion. SB-277011-A (R&D Systems, Minneapolis) was dissolved in a solution of 10% hydroxypropyl-b-cyclodextrin in sterile water, administered intraperitoneally in a volume of 2 ml/kg 30 min prior to the test session. The time chosen for SB-277011-A administration was based in previous published literature (Vorel et al., 2002).

2.3. Apparatus

2.3.1. Context A

Rats were tested in operant chambers (MED Associates; 29.5 cm × 32.5 cm × 23.5 cm). Three sides were constructed from Plexiglas, and the fourth was made of stainless steel, on which two 4 cm-wide retractable levers were secured. The two levers were 12 cm apart, and 8 cm from the grid floor. Above each lever there was a cue light (2.5 W, 24 V), and a houselight (2.5 W, 24 V) was located on the opposite wall. The floor of the chamber was composed of a metal grid. A Silastic tubing shielded with a metal spring extended from each intravenous catheter to a liquid swivel (Stoelting, Wood Dale, IL) mounted on an arm fixed outside of the operant chamber. Tygon tubing extended from the swivel to a Razel infusion pump (Semat Technical Ltd., Herts, UK) located adjacent to the external chamber. The testing chamber was placed within a sound- and light-attenuating box, equipped with a ventilation fan that also screened external noise. The doors of the attenuating box remained closed and the room lights were off during the sessions.

2.3.2. Context B

The extinction context was an operant chamber that is taller than the training box of context A (40 cm × 30 cm × 40 cm), with walls that were patterned (vertical black and white stripes) instead of clear walls and floors that were box grids instead of bars. Differences in wall pattern and floor texture are classic variables in studies of context-type studies such as place preference where animals clearly demonstrate that they can distinguish the two contexts (Cunningham et al., 2003; Sabioni et al., 2012; White and Carr, 1985). The chamber was placed within a sound- and light-attenuating box (78 cm × 50 cm × 50 cm). There was no houselight in the chamber, no fan and the doors of the attenuating box remained open during the extinction sessions (room lights off). The levers did not retract.

2.4. Food training

Rats were trained to lever press for food prior to the nicotine self-administration sessions. The apparatus was the same as described in the Context A, except that there was a receptacle positioned between the two levers that the rats received a food pellet (45-mg precision pellets; Bioserv, Laurel, Maryland), absent in the chambers from Context A. During the food training sessions, the house light was on and each lever press resulted in a food pellet alone. The purpose of this training was to establish operant responding. The sessions were 1 h in length for at least 5 days until animals reached criterion, defined as 100 food pellets within a 20 min interval.

2.5. Intravenous surgery

Rats were anaesthetized with isoflurane gas anaesthesia and implanted in the right jugular vein with a catheter (Silastic tubing with a polypropylene knitted mesh, CamCaths©, Cambridge, UK). Briefly, the catheter was inserted in the jugular vein, and passed subcutaneoulsly to the dorsal surface between the scapulae where it exited (Gamaleddin et al., 2013). Derapen was used prophylactically in a dose of 30,000 units s.c. 3 times per week starting at least 3 days prior to the surgery and at least 3 times in the week following the surgery. Animals underwent a 1–2 week recovery period prior to the commencement of experimental procedures. From the second day following the surgery until the end of the acquisition phase of the self-administration sessions, the catheters were flushed 5–7 times a week with saline containing heparin (0.1 ml, 30 USP units/ml). Catheter patency was tested periodically with the short-acting barbiturate methohexital sodium (0.1 ml of 10 mg/ml solution, i.v.).