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Nicotine enhances the expression of a sucrose or cocaine conditioned place preference in adult male rats

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ABSTRACT

Nicotine has been shown to enhance the motivational properties of non-nicotine stimuli. This reinforcement-enhancing property of nicotine has the potential to promote the use of other illicit substances as well as maladaptive patterns of food intake. Therefore, the current study aimed to examine whether nicotine enhances preference for contexts paired with cocaine or sucrose utilizing a place conditioning procedure. Separate groups of adult male rats were administered with sucrose or cocaine in one of two compartments of a standard CPP chamber in four consecutive days. Preference was then assessed following no injection, a single subcutaneous (s.c.) injection of nicotine, and a s.c. saline injection. The animals preferred the chamber paired with either sucrose or cocaine, as evident from an increased time spent in the paired chamber compared to baseline. Nicotine further increased the time spent in the sucrose- or cocaine-paired chamber, consistent with a reinforcement-enhancement effect. Previous results demonstrate an interaction between nicotine and intake of other drugs or food. The present findings provide an additional mechanism that may underlie these effects and which may have implications for drug dependence and obesity.

1. Introduction

Despite widespread knowledge of its negative health consequences, tobacco use constitutes the leading cause of preventable death in the United States (Centers for Disease Control and Prevention, 2011). Research into the reinforcing effects of nicotine suggests that while nicotine, the principal reinforcing agent in tobacco, is important in sustained tobacco dependence (Anthony et al., 1994; Caggiula et al., 2001; Goldberg et al., 1981; Rose and Corrigall, 1997), environmental stimuli play a critical role in nicotine reinforcement (Bevins and Caggiula, 2009; Conklin and Tiffany, 2001; Rose et al., 2000). This work has demonstrated both the ability of nicotine to transform neutral, non-drug stimuli into conditioned reinforcers (Geier et al., 2000; Palmatier et al., 2007a; Perkins et al., 1994; Rose and Behm, 1991; Rose and Levin, 1991) and the ability of nicotine to non-associatively enhance responding for other reinforcers (Barret and Bevins, 2013; Barrett and Bevins, 2012; Caggiula et al., 2009; Chaudhri et al., 2006b; Palmatier et al., 2006). Like nicotine, other drug of abuse, particularly psychostimulants, also impact the reinforcing properties of other stimuli through both associative and non-associative effects (Chaudhri et al., 2006b; Graves and Napier; Weiss et al., 2000; Zhou et al., 2005).

The reinforcement-enhancing property of nicotine may promote the use of other substances such as rewarding, palatable food or other drugs of abuse. It has previously been demonstrated in preclinical investigations that prolonged nicotine exposure enhances sensitization and conditioned place preference to cocaine, as well as multiple markers of neuronal activity following cocaine (Levine et al., 2011). Likewise, both clinical and preclinical evidence point to interactions between nicotine and other drugs of abuse (Doyon et al., 2013; Huang et al., 2013; Levine et al., 2011; Richter et al., 2002). For example, cigarette smoking may intensify the subjective effects of cocaine and cocaine craving (Brewer et al., 2013) and clinical data suggest a negative relationship between smoking and cocaine abstinence (Shoptaw et al., 1996). Nicotine also affects feeding behaviors (Jo et al., 2002). Nicotine has anorectic effects on food consumption (Wellman et al., 2005) in rats, but increases operant responding for sucrose pellets (Palmatier et al., 2012; Schassburger et al., 2013) or solution (Barret and Bevins, 2013), which may indicate enhanced motivation to respond for palatable food (Donny et al., 2011).

Although nicotine is known to enhance responding for drugs of abuse and palatable food, studies of the interaction between nicotine and reward-paired stimuli are limited. These studies are important

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because they can provide insight into the manner in which nicotine impacts reinforced behavior. For example, nicotine may alter the likelihood of seeking out contexts predictive of reinforcement independent of any action on the rewarding outcome associated with the drug or food. The current study tested this hypothesis by examining the ability of nicotine to enhance a context paired with either sucrose or cocaine.

We utilized a place conditioning procedure to investigate this interaction between nicotine and food or drug cues. The bulk of the work to date examining the nicotine reinforcement-enhancing effect has exclusively used behavioral models involving an operant response (but see Thiel et al. (2009)). While some of this work has made significant progress in delineating varied mechanisms by which nicotine may increase responding for non-nicotine reinforcers (Barret and Bevins, 2013; Cassidy and Dallery, 2012), the evaluation of acquisition and expression of learned associations less clear in operant behavioral procedures, and nicotine's effects on locomotor activity may serve as a confounding variable. Therefore, the ability to examine the reinforcement-enhancing effects of nicotine in alternative models would be highly useful. The designed experiments address whether nicotine enhances the expression of a preference for sucrose or drug-paired cues, while simultaneously demonstrating whether such investigations are feasible using a place conditioning procedure. We predicted that a single s.c. injection of nicotine could enhance the preference for environments associated with palatable food or drug reward.

2. Materials and methods

2.1. Subjects

Male, Sprague–Dawley rats (n = 36, Harlan Farms, Indianapolis, IN), were ordered to weigh 200–225 g upon arrival, were singly housed in suspended, wire mesh cages in a temperature and humidity-controlled colony room on a reversed light/dark cycle (lights off 7 am) with ad lib access to food and water. They were handled and weighed daily, and weights ranged between 265 and 317 g throughout testing. All conditioning and testing took place during the dark hours of the cycle. After one week of acclimatization, the rats remained on ad lib water but were food restricted to 20 g of food per day. Rats in the cocaine CPP study remained on this diet for the duration of the experiment, whereas animals in the sucrose CPP study were further restricted to 15 g of food per day prior to initial sucrose exposure through the duration of the experiment. This measure was taken to encourage sucrose consumption during the conditioning phase of the study. Practices utilized in this study were approved by the University of Pittsburgh Institutional Animal Care and Use Committee (IACUC) and carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

Cocaine hydrochloride (Sigma, St. Louis, MO) was dissolved in sterile 0.9% saline solution. A 10 mg/kg/ml dose was selected based on previous studies demonstrating cocaine CPP (Harris and Aston-Jones, 2003). Nicotine hydrogen tartrate (Sigma, St. Louis, MO) was dissolved in 0.9% saline solution. The pH of the solution was adjusted to 7.0 (+0.2) using dilute NaOH. The dose of nicotine used was 0.4 mg/kg/ml (free base concentration) based on the results of previous studies demonstrating the reinforcement-enhancing effects of subcutaneous nicotine injections (Caggiula et al., 2009; Wing and Shoaib, 2010). Both nicotine and cocaine solutions were passed through a 0.22 μm filter to ensure sterility.

2.3. Sucrose pre-exposure

Rats designated as part of the sucrose CPP experiment received two, 2-h exposures to 25% sucrose in their home cage to reduce novelty-induced hypophagia. The percent sucrose solution was chosen based on previous literature (White and Carr, 1985), with the goal of attaining a modest preference to allow for measurement of a possible nicotine-enhancement effect. Sucrose was made by dissolving crystalline sucrose (Fisher Scientific, Waltham, MA) in tap water. Bottles were placed opposite cage water bottles during sucrose exposure. Bottles were weighed before and after sucrose exposure to measure sucrose consumption.

2.4. Place conditioning

2.4.1. Conditioned place preference chamber

Rats were conditioned and tested in CPP chambers (MED-CPP-RS, Med Associates, Inc., St. Albans, VT). Each chamber had three compartments with distinct wall patterns and floor textures. Compartments A and B were equal in size and dimension and were separated by a small middle compartment. Manually operated guillotine doors separated all compartments. Lighting in compartments A and B were set at 0.2 lx each, whereas center chamber lighting was set to 8.3 lx to reduce inherent preference for the small, center compartment. Infra-red photo beam sensors in each chamber recorded how much time the animal spent in each compartment during testing. Each chamber was encased in a sound-attenuating cabinet.

2.4.2. Initial preference assessment

On day 1, all animals underwent a 20 min initial preference assessment to establish baseline preference. Manually operated guillotine doors were open during the testing to allow free access to all chamber compartments. Rats were placed into the center compartment, allowed to freely explore for 20 min, and then removed and returned to their home cage. Time spent in each compartment was recorded. Rats (n = 9) that spent more than 60% of their time in any single chamber during the initial preference test were excluded from the study and not subject to further procedures to maintain minimal contribution of novelty-seeking or extreme bias to the procedures. Rats were randomly assigned to sucrose (n = 14) or cocaine (n = 13) conditioning groups.

2.4.3. Conditioning sessions: sucrose

Conditioning sessions were counterbalanced by order and UCS-paired compartment (random, nonbiased design) and conducted over 4 days with one UCS and one control session per day separated by 4 h. The rats were placed directly into the conditioning compartment. Ten minutes into each UCS conditioning session, bottles were inserted into CPP compartments (control session — empty, sucrose session — 25% sucrose). The rats were removed and returned to the home cage after another 10 min (20 min total session).

2.4.4. Preference tests: sucrose

Three preference tests were conducted on consecutive days 24 h after conditioning was complete. For each test, the rats were placed into the center compartment of the apparatus and left undisturbed with free access to all compartments (no bottles present) for 20 min. Five minutes prior to preference test 2, each animal received a single injection of 0.4 mg/kg nicotine. Five minutes before preference test 3, each animal received a 0.3 ml injection of 0.9% saline. The animals spent the 5 min between s.c. injections and the start of preference tests in their home cages. The rats were returned to their home cage after completion of the 20 min test. Time spent in each compartment was recorded.

2.4.5. Conditioning sessions: cocaine

Conditioning sessions were counterbalanced by order and UCS-paired compartment (random, nonbiased design) and conducted over 4 days with one UCS and one control session per day separated by 4 h. This allowed for minimal carryover of cocaine effects to the control session due to the short half-life of cocaine (Sun et al., 2002). Rats began each conditioning session with a cocaine (10 mg/kg/ml, i.p.) or

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