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The incentive amplifying effects of nicotine are reduced by selective and non-selective dopamine antagonists in rats

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ABSTRACT

Nicotine is a psychomotor stimulant with 'reinforcement enhancing' effects — the actions of nicotine in the brain increase responding for non-nicotine rewards. We hypothesized that this latter effect of nicotine depends on increased incentive properties of anticipatory cues; consistent with this hypothesis, multiple laboratories have reported that nicotine increases sign tracking, i.e. approach to a conditioned stimulus (CS), in Pavlovian conditioned-approach tasks. Incentive motivation and sign tracking are mediated by mesolimbic dopamine (DA) transmission and nicotine facilitates mesolimbic DA release. Therefore, we hypothesized that the incentive-promoting effects of nicotine would be impaired by DA antagonists. To test this hypothesis, separate groups of rats were injected with nicotine (0.4 mg/kg base) or saline prior to Pavlovian conditioning sessions in which a CS (30 s illumination of a light or presentation of a lever) was immediately followed by a sweet reward delivered in an adjacent location. Both saline and nicotine pretreated rats exhibited similar levels of conditioned approach to the reward location (goal tracking), but nicotine pretreatment significantly increased approach to the CS (sign tracking), regardless of type (lever or light). The DA_{D1} antagonist SCH-23390 and the $DA_{D2/3}$ antagonist eticlopride reduced conditioned approach in all rats, but specifically reduced goal tracking in the saline pretreated rats and sign tracking in the nicotine pretreated rats. The non-selective DA antagonist flupenthixol reduced sign-tracking in nicotine rats at all doses tested; however, only the highest dose of flupenthixol reduced goal tracking in both nicotine and saline groups. The reductions in conditioned approach behavior, especially those by SCH-23390, were dissociated from simple motor suppressant effects of the antagonists. These experiments are the first to investigate the effects of dopaminergic drugs on the facilitation of sign-tracking engendered by nicotine and they implicate dopaminergic systems both in conditioned approach as well as the incentive-promoting effects of nicotine.

1. Introduction

Nicotine, one of the most widely used addictive substances in the world (Ague, 1972; Lerman and Audrain-McGovern, 2010), is considered to be the reinforcing agent in tobacco products (USDHHS, 1988). Several lines of evidence suggest that nicotine plays a critical role in smoking and other forms of tobacco use (Chaudhri et al., 2006; Rose, 2006; Caggiula et al., 2009; Le Foll and Goldberg, 2009). Nicotine supports operant behavior in humans (Perkins et al., 2001) as well as several non-human species (Henningfield and Goldberg, 1983). Nicotine replacement therapies are one of the most widely used treatments for smoking cessation and they improve cessation rates by 50–70% (Stead et al., 2012). Also, cessation products that do not include nicotine or include nicotine reduction (e.g., Quest® cigarettes) have been commercial failures, whereas smoke-free cigarettes that provide a nicotine vapor, while not accepted as cessation therapies, are gaining market share as alternatives to tobacco delivery products (Odum et al., 2012).

The central role of nicotine in tobacco dependence is undeniable; however, the role of nicotine in dependence may not be as straightforward as with other abused drugs. Nicotine is a moderate stimulant with weak and unreliable reinforcing properties (Caggiula et al., 2009). While nicotine infusions by themselves support operant behavior in non-human animals (Donny et al., 2003); the effects of nicotine are weak, and under progressive-ratio reinforcement schedules the motivation to obtain nicotine infusions is relatively low (Chaudhri et al., 2007). In choice situations, nicotine is less preferred than other abused drugs, such as cocaine (Manzardo et al., 2002). Despite its relatively low reinforcing efficacy, responding for nicotine is robustly enhanced by inclusion of other environmental stimuli (Palmatier et al., 2006). For example, visual reinforcers included with nicotine infusions increase operant responding (Donny et al., 2003) and motivation to obtain

Abbreviations: bHR, bred for high responsiveness to novel environments; bLR, bred for low responsiveness to novel environments; CS, conditioned stimulus; DA, dopamine; NIC, nicotine; SAL, saline; US, unconditioned stimulus.

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the reinforcer(s) (Chaudhri et al., 2007). This interaction between nicotine and non-nicotine stimuli has recently been replicated in human smokers (Perkins and Karelitz, 2013a,b). Also, human research suggests that the 'euphoric' effects of nicotine self-administered in cigarettes are weak and their subjective pleasure may be heavily influenced by environmental factors (Dar et al., 2007) and that individuals with high reactivity to food-associated cues also have high reactivity to nicotine-associated cues (Mahler and de Wit, 2010).

Evidence from our laboratory and others has stressed that incentive motivation may be critical to the interaction between nicotine and non-nicotine stimuli (Olausson et al., 2004a, 2004b; Palmatier et al., 2012, 2013; Peartree et al., 2012). For example, we recently found that nicotine-induced increases in motivation in an operant task did not depend on the strength of the reinforcer used, but was exquisitely sensitive to the strength of the 'cues' associated with that reinforcer (Palmatier et al., 2013). We also found that nicotine increased approach to a conditioned stimulus (CS) that was spatially separated from an unconditioned stimulus (US) in a Pavlovian conditioned approach task (Palmatier et al., 2012). This increase in 'sign tracking' (i.e., approach to CS) was not accompanied by a change in approach to the US ('goal tracking'), and the nicotine-induced increase in sign tracking was systematically related to in the intensity of the US. Specifically, greater nicotine-induced increases in sign tracking were observed when the CS was paired with 20% sucrose, relative to rats that had the CS paired with 5% sucrose. Collectively, these findings suggest that nicotine increases incentive-based motivation, which may help to explain why the reinforcing (Donny et al., 2003; Chen et al., 2011) and rewarding (Peartree et al., 2012) effects of nicotine are more robust when non-nicotine reinforcers and rewards are included in the test paradigm.

Incentive motivation is widely considered to depend on the mesotelencephalic dopamine (DA) system (Berridge and Robinson, 1998; Wightman and Robinson, 2002; Uslaner et al., 2008; Flagel et al., 2011; Saunders and Robinson, 2012; Anselme et al., 2013). For example, in selectively bred rats that display more sign tracking behavior, phasic DA responses to a CS are more pronounced in the core of the nucleus accumbens (NAc). Systemic administration of the non-selective DA antagonist flupenthixol reduces acquisition of sign tracking in these rats (Flagel et al., 2011). Reduced expression of sign tracking was observed after local administration of flupenthixol to the NAc (Saunders and Robinson, 2012). Also, genetic reconstruction of D_1-receptor function in the NAc core in DA D_1 receptor knock-out mice preferentially increased acquisition of sign-tracking responses, whereas reconstruction of D_1 function in the NAc shell did not restore sign- or goal-directed conditioned responses (Gore and Zweifel, 2013). Thus, the NAc, and in particular DA D_1 receptors in the core, appear to play a critical role in the acquisition and expression of sign tracking.

We hypothesized that nicotine-facilitated sign tracking is dependent on mesolimbic DA transmission. To address this hypothesis, we replicated our previous findings in which injections of nicotine prior to testing sessions increase approach to a CS paired with a sweet reward. In Experiment 1, the CS (30 s presentation of a light) was presented inside of a receptacle that could monitor approach (head entries). The US (0.1 ml presentation of 5% chocolate solution) was delivered in a separate, identical receptacle in which head entries could also be monitored. Once we established that nicotine increased approach to the CS, we investigated the role of DA receptors by pre-treating rats with the D_1 receptor antagonist SCH-23390, the $D_{2/3}$ receptor antagonist eticlopride, and the non-selective DA receptor antagonist flupenthixol. A video-recording system installed in the testing chambers and automated behavioral monitoring software were used to monitor approach and non-specific effects of the antagonists. In Experiment 2 the findings from Experiment 1 were confirmed with a CS that is more comparable to previous studies of sign tracking — a lever was inserted into the chamber for 30 s and a light above the lever was illuminated. Sucrose solution (20% w/v) served as the US in Experiment 2.

2. Method

2.1. Subjects

2.1.1. Experiment 1

Ten male Sprague Dawley rats weighing 274–300 were purchased from Charles River Laboratories (Raleigh, NC) and were housed in a temperature- and humidity-controlled environment. The rats were non-naïve, as they initially participated as control subjects in a previous operant-conditioning experiment with a sucrose reinforcer (20% w/v). In that study, rats were randomly assigned to NIC (0.4 mg/kg nicotine) or SAL (vehicle) exposure conditions ($n = 5$/group). Rats in both groups received 24 sessions (approximately 1 h per day) in the operant test chambers and the NIC group received 26 exposures to nicotine, but these injections were temporally separated from chamber exposures (at least 1 h after sessions). To reduce generalization between studies, the rats were shifted to new chambers, the levers were removed, and Nesquick® chocolate was used as the US. In the original study, sucrose was delivered in a liquid dipper for pressing a lever located on one wall of the chamber. For the present study, the CS and US locations were on the opposite wall and Nesquick was delivered via syringe pump to a receptacle well (see Apparatus). All rats had water ad libitum and were fed 20 g food per day, after the daily conditioning session.

2.1.2. Experiment 2

Sixteen male Sprague Dawley rats weighing 274–300 were purchased from Charles River Laboratories (Raleigh, NC) and were housed in the same manner as Experiment 1. All rats in Experiment 2 were naïve before acquisition.

2.1.3. Drugs and solutions

Nicotine hydrogen tartrate salt was purchased from Sigma-Aldrich (St. Louis, MO) and mixed in sterile saline, the pH was adjusted to 7.0 ($\pm$0.2) with a dilute NaOH solution. Nicotine dose (0.4 mg/kg) was calculated from the freebase form and the solution was injected subcutaneously 15 min before testing sessions unless otherwise noted. SCH-23390, (−)-eticlopride hydrochloride, and flupenthixol dihydrochloride were purchased from R&D Systems (Minneapolis, MN) and mixed in sterile saline. All DA antagonists were injected into the intraperitoneal cavity (ip) 30 min before test sessions. Powdered Nesquick® (chocolate) was purchased from a local market and dissolved in tap water at a concentration of 5% (w/v).

2.1.4. Apparatus

Ten standard modular operant chambers housed in sound attenuating cubicles were used in this experiment. The chambers, cubicles, interfacing and software were purchased from Med Associates (St Albans, VT). Each chamber had two walls fitted with three modular panels for intelligence devices. One of the walls was fitted with two receptacles equipped with LED panel lamps and infrared head-entry detectors, a liquid well and an 18 g pipe for fluid delivery. In Experiment 1, fluid was delivered to the US receptacle via syringe pump (Razel Scientific, St. Albans, VT) with a 10 RPM motor, and the syringe was fitted with a blunted 18 g needle and connected to the US receptacle with Tygon chemical resistant microbore tubing (10.16 mm, ID). The syringe pump was programmed to deliver 0.1 ml of the Nesquick® solution for each US presentation. The receptacles were located on the left and center panels of the wall. Because of the size of the head-entry detector units, the height of each receptacle had to be offset — the left receptacle was mounted slightly lower, with the bottom edge approximately 1.5 cm above the floor of the chamber, the right receptacle was higher, with the bottom edge located 6 cm above the floor. The light stimuli were Dialight LED panel lamps (white, 20 mA, 100 fL luminous intensity) purchased from Newark-Element 14 (Newark, NJ). The opposite wall was fitted with a liquid dipper and head entry receptacle (center panel), two levers and stimulus lights located above each lever (left