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Adolescent exposure to nicotine results in reinforcement enhancement but does not affect adult responding in rats

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ABSTRACT

Background: Adolescence is a period of development associated with a peak in an organism's responsiveness to reward. Epidemiological data indicate that the initiation of smoking is high during adolescence and that earlier age of onset is associated with increased incidence of dependence as adults. In rats, nicotine is known to have primary reinforcing and reinforcement enhancing effects. Although the primary reinforcing effects of nicotine have been demonstrated in adolescent rats (self-administration), less is known about its reinforcement enhancing effects during this period. Moreover, the impact of adolescent nicotine exposure on its reinforcement enhancing effects during adulthood has not yet been examined. The objectives of this study were to assess whether (1) nicotine enhances operant responding for an unconditioned visual reinforcer (VS) in adolescent rats, and (2) exposure to nicotine during adolescence affects responsiveness to the VS in adulthood.
Methods: Rats were exposed to nicotine (0.32 mg/kg, subcutaneous injection) or saline during adolescence (postnatal day 29–42) and adulthood. Nose-poking for the VS was assessed under fixed and progressive ratio schedules.
Results: Nicotine increased responding for the VS during adolescence. Adolescent nicotine exposure failed to significantly affect adult responsiveness for the VS, regardless of adult nicotine exposure, but early exposure to the VS affected responsiveness to the VS in adulthood.
Conclusions: Nicotine exhibits reinforcement enhancing effects in adolescent rats. Long-term effects of adolescent nicotine on reinforcement enhancement are minimal, but the impact of early exposure to the VS and/or the primary reinforcing effects of nicotine requires further investigation.

1. Introduction

Adolescent cigarette smoking is a major and persistent public health problem. Almost invariably, smoking begins during adolescence and those individuals who progress to daily smoking typically do so by age 18 (Clarke, 1998). Worldwide, nearly 5 million smokers die prematurely each year due to tobacco-related illnesses. Given that a majority of these individuals started smoking as adolescents, the need for a better understanding of the proximal and long-term consequences of adolescent nicotine exposure is urgent.

Addiction to nicotine, the primary psychoactive substance in tobacco, is widely regarded as a necessary factor sustaining cigarette use. Nicotine, similar to other drugs of abuse, acts to reinforce behavior related to its use and confers potent incentive properties to nicotine-related stimuli (primary reinforcement; Corrigall and Coen, 1989; Donny et al., 1998; Shoaib et al., 1997). Additionally, nicotine enhances the efficacy of concurrently available reinforcers through a non-associative mechanism (reinforcement enhancement; Donny et al., 2003; Palmatier et al., 2006). Hence, both the primary reinforcement and reinforcement enhancement properties of nicotine may contribute to smoking and other forms of tobacco use (a "dual reinforcement" model; Caggiula et al., 2009; Chaudhri et al., 2006).

The dual reinforcement model likely has important implications for understanding nicotine self-administration and smoking during adolescence, a developmental period characterized by normative increases in reward responsiveness (Doremus-Fitzwater et al., 2010). Indeed, several preclinical studies have shown that adolescents may have increased responsiveness to the primary reinforcing effects of nicotine (Barron et al., 2005; O'Dell, 2009; Spear, 2000). Most self-administration studies report that adolescent rats are more responsive to nicotine than similarly

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treated adult rats (Adriani et al., 2003; Chen et al., 2007; Levin et al., 2003, 2007), with notable exceptions reported by Shram and colleagues (2008a,b,c). Similarly, increased adolescent responsiveness to the conditioned rewarding effects of nicotine has been exhibited using the conditioned place preference paradigm (Shram and Le, 2010; Tzschentke, 2007). Considerably less is known about nicotine-related reinforcement enhancement during adolescence. Using adolescent rats, Thiel and colleagues (2009) showed that nicotine and social reward synergistically interacted to enhance conditioned place preferences (CPP) above levels produced when the stimuli were presented separately. However, this effect has yet to be observed using an operant paradigm.

Moreover, it has been suggested that adolescent exposure to nicotine may enhance responsiveness to nicotine reward later during adulthood (O'Dell, 2009). This assertion is in line with epidemiological evidence indicating that individuals who smoke during adolescence have an elevated risk of nicotine dependence and a reduced likelihood of quitting as adults (Breslau and Peterson, 1996; Adelman, 2006; Nelson et al., 2008). Increased adulthood responsiveness to nicotine reward as a result of adolescent nicotine exposure in rats has been observed using several different paradigms, including self-administration (Levin et al., 2003), response-independent administration (Adriani et al., 2003), and conditioned place preference (Adriani et al., 2006). To our knowledge, however, no study has examined whether adolescent nicotine exposure affects the reinforcement enhancing effect during adulthood.

The purpose of the current study was to extend the existing adolescent preclinical literature in two important ways. First, we examined the reinforcement enhancement effect in adolescent rats by using an operant procedure to determine if nicotine treatment results in enhanced responding for an unconditioned visual reinforcer (VS). Second, we examined whether adult responding for the VS would be altered by prior exposure to nicotine during adolescence.

2. Methods

2.1. Subjects

The current experiment included 120 male Sprague-Dawley rats (bred at Harlan Farms); rats were shipped on PND 20 and arrived on PND 21, weighing 35–65 g (mean ± SD: 51.2 ± 6.6 g). Rats were individually housed under a 12 h reversed dark/light cycle immediately upon arrival. After three days of unlimited access to food (Lab Diet 5001, PMI Nutrition International, Brentwood, MO) rations were restricted to 20 g/day, but adolescent rats did not consume this full amount until PND 28–30. Unlimited access to water was available in home-cages.

2.2. Apparatus

Sessions occurred in eighteen operant-conditioning chambers (Med Associates model ENV-008CT, St. Albans, VT). Two nose-poke receptacles, equipped with infrared emitter/detector units (Med Associates model ENV-114BM, St. Albans, VT), were horizontally aligned 3 cm above the floor. Stimulus-lights (125-V) were located 5 cm above each nose-poke operandum. A house-light (28-V) was centrally adjacent to the ceiling on the opposite wall. Chambers were enclosed in sound attenuating cubicles and extraneous sounds were masked by an internal exhaust fans. Events were arranged and recorded by Med-PC® software (Med Associates, St. Albans, VT).

2.3. Nicotine/saline doses

Nicotine bitartrate (doses expressed as free base) was dissolved into 0.9% saline solution and the pH was adjusted to 7.0 (±0.2) with NaOH. Nicotine (0.32 mg/kg) or saline was delivered via subcutaneous (SC) injection at a volume of 1 ml/kg. Injections occurred immediately before the session. The dose of nicotine was determined in pilot studies that examined the dose-response function (0.1–1.0 mg/kg) for rats ranging from postnatal day (PND) 28–42. These studies found 0.32 mg/kg nicotine produced near maximal responding for the VS (see below for complete description); larger doses resulted in similar effects (i.e., a monophasic dose–response function).

Table 1
Procedures for all groups.

Group	Adolescent phase		Adult phase		
	Drug	VS	Drug	VS	N
1. NIC(VS)/NIC(VS)	NIC	YES	NIC	YES	15
2. NIC(VS)/SAL(VS)	NIC	YES	SAL	YES	15
3. SAL(VS)/NIC(VS)	SAL	YES	NIC	YES	15
4. SAL(VS)/SAL(VS)	SAL	YES	SAL	YES	15
5. NIC/NIC(VS)	NIC	NO	NIC	YES	15
6. NIC/SAL(VS)	NIC	NO	SAL	YES	15
7. SAL/NIC(VS)	SAL	NO	NIC	YES	15
8. SAL/SAL(VS)	SAL	NO	SAL	YES	15

2.4. Behavioral procedures

Experimentation began with one 20-min chamber habituation session, where programmed stimuli were unavailable. All subsequent sessions lasted 65 min. The first 5-min did not involve any programmed consequences, but allowed for drug absorption and chamber acclimation. Experimental contingencies began after the 5-min period and were signaled by the illumination of the house-light.

Nose-poke response acquisition began the day after chamber habituation, and occurred over four daily sessions (PND 25–28). No response shaping occurred before the response acquisition phase. Acquisition began with responding under a fixed ratio 1 schedule (FR 1) (PND 25) followed by an FR 2 (PND 26–28). The nose-poke operandum associated with reinforcement ("active") was randomly assigned. Reinforcement was a compound unconditioned visual stimulus (VS) that included a 1-s stimulus-light onset followed by a 1-min house-light offset. Responses during the VS were recorded, but had no programmed consequence. Responses on the alternative nose-poke operandum ("inactive") were recorded, but did not result in programmed reinforcers. Following acquisition, animals were assigned to one of eight groups that were counterbalanced according to active operandum assignment and rate of active nose-pokes over the last two days of the acquisition phase (PND 27–28).

Experimental groups ($n = 15$/group) were differentiated according to their history of exposure to VS contingencies, nicotine during adolescence, and nicotine exposure during adulthood (Table 1). Groups assigned to "VS-experimental" contingencies during adolescence were reinforced for nose-poking in the active operandum. Groups assigned to adolescent "VS-control" contingencies were placed in the operant chamber without any programmed stimuli for the duration of the session. Responding was reinforced by the VS in all groups during adulthood. Adolescence was defined as PND 29–42 (Spear, 2000). During adolescence, animals were tested 7 days/week under FR (PND 29–39) and progressive ratio (PR) (PND 40–42) schedules of reinforcement. During adulthood, experimental sessions occurred 5 days/week from PND 64–79, with the PR schedule in place during PND 70–72. No tests occurred between PND 43 and 63, but animals were weighed and handled regularly.

2.5. Data analysis

The main dependent variable and focus of analysis was the total number of VS presentations earned (i.e., reinforcers) during the session. The results using response rates were consistent with VS reinforcement rates.

Statistical analyses of VS presentations were conducted using mixed-model analysis of variance (ANOVAs) with within-subject factors of Session or Phase (Adolescent or Adult), and a combination of the following between-subject factors: Operandum (active or inactive), Adolescent Drug (nicotine or saline), Adult Drug (nicotine or saline), and/or VS History (VS or no VS). All estimates of the effect of Session (FR only) were specified using linear contrasts. In some cases pairwise post hoc comparisons were used with Bonferroni's correction to evaluate significant main effects or interactions where appropriate. Alpha levels were set to $p < 0.05$. It should be noted that due to technical issues half the rats were not run on PND 32 and 34–36 and those animals were omitted from the data analysis on those days.

3. Results

3.1. Active responding

Overall, active responses were significantly greater than inactive responses (FR: $F_{1,236} = 95.2$, $p < 0.001$, PR: $F_{1,236} = 30.3$, $p < 0.001$) and this effect was consistent across experimental phases. Additional pairwise comparisons were made for each phase and were consistent with the overall findings.