Published in final edited form as:

Drug Alcohol Depend. 2012 October 1; 125(3): 307–312. doi:10.1016/j.drugalcdep.2012.03.006.

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.

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Contributors: All authors meet the criteria for authorship and approve of the final manuscript. Author #1 design the study, wrote the protocol, undertook statistical analysis, wrote the introduction, methods, and results, and the final draft of the entire manuscript. Author #2 wrote the discussion section. Authors #3–6 helped design, implement and analyze the experiment and assisted with the writing of the manuscript.

Conflicts of Interest: The authors have no disclosures or conflicts of interest to report.

Keywords

Nicotine; Adolescent; Reinforcement; Reinforcement Enhancement; Rat; Nose-poke; Operant Behavior

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 (Clark, 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 treated adult rats (Adriani et al., 2003; Chen et al., 2007; Levin et al., 2007; Levin et al., 2003), with notable exceptions reported by Shram and colleagues (2008a; 2008b; 2008c). 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 to 65 g (mean $\pm$ SD: 51.2 $\pm$ 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 PND28–30. 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 ($\pm$ 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 to 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).

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 ($n=15/\text{group}$) 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.

3.2 Adolescent Phase

Injections of nicotine increased reinforcer presentations in both FR and PR schedules (Figure 1 and 2). The omnibus ANOVA revealed a significant effect of Adolescent Drug under FR ($F_{1,58} = 33.5$, $p < 0.001$) and PR schedules ($F_{1,58} = 24.9$, $p < 0.001$). Additionally, significant linear Adolescent Drug by Session interactions during the FR sessions indicated that reinforcement presentations increased in the nicotine groups over sessions while the saline groups remained stable ($F_{1,58} = 18.7$, $p < 0.001$; Figure 1).

3.3 Adult Phase

Adult nicotine exposure enhanced VS reinforcement. The number of reinforcers earned under the FR and PR were significantly greater in the nicotine groups than in the saline groups (FR: $F_{1,112} = 208.3$, $p < 0.001$, PR: $F_{1,112} = 128.5$, $p < 0.001$) (Figure 1). These FR differences grew linearly over repeated sessions ($F_{1,112} = 68.2$, $p < 0.001$).

Adolescent nicotine exposure did not result in significant changes in responding for the VS during adulthood. Analyses failed to indicate an effect of Adolescent Drug or any interactions in either the FR or PR.

Adolescent exposure to the VS did alter the rate of VS reinforcement in adults. Animals with a history of responding for the VS during adolescence had higher reinforcement rates (on both FR and PR schedules) than those lacking a VS History (FR: $F_{1,112} = 169.2$, $p < 0.001$; PR: $F_{1,112} = 71.6$, $p < 0.001$) (Figures 1 and 2). Furthermore, a steeper increase over sessions in the animals without a VS history resulted in a VS History by Session interaction ($F_{1,112} = 149.5$, $p < 0.001$). However, the effect of Adult Drug did not vary significantly as a function of VS History. There was also a three way interaction between Adolescent Drug, Adolescent VS History, and linear Day ($F_{1,112} = 4.8$, $p < 0.05$). Additionally, adolescent and adult phases were collapsed across the final three days and analyzed to further address the impact of the VS (Figure 3). The omnibus ANOVA revealed a significant effect of Phase ($F_{1,56} = 120.3$, $p < 0.001$). An ANOVA restricted to the adolescent phase showed a significant effect of Adolescent Drug ($F_{1,56} = 120.3$, $p < 0.001$). An ANOVA restricted to the adult phase revealed a significant effect of VS History ($F_{1,112} = 17.6$, $p < 0.001$) and Adult Drug ($F_{1,112} = 188.3$, $p < 0.001$), but no interaction between the two factors.

4. Discussion

4.1 Nicotine Effects during Adolescence

Similar to adults (Palmatier et al., 2009), adolescent rats exhibited reinforcement enhancing effects of nicotine. Rats pretreated with nicotine showed enhanced responding and earned more visual reinforcers (VS) than those injected with saline. As seen in Figure 1A, this effect emerged across sessions, with clear divergence between nicotine and saline groups by session seven. To our knowledge, these data are the first to demonstrate the reinforcement enhancing effect of nicotine in adolescent rats using an operant procedure.

It remains unclear whether adolescents are more or less sensitive than adults in terms of the reinforcement enhancing effects of nicotine, as this study was not designed to make a direct comparison between age groups. These initial data, however, do suggest similar effects for developmental stages when compared to our previous findings (i.e., Palmatier et al., 2009) and those reported in Figure 1B for animals naive to nicotine before adulthood (cf., response rates for adolescents responding under the influence of nicotine and the SAL/NIC(VS) group). Still, strong conclusions regarding developmental similarities or differences in the reinforcement-enhancing effects of nicotine would require careful consideration of several factors, including potential differences in the baseline rates of responding, the reinforcing value of the VS, the dose-response relationship, and the effort required to make a response.

4.2 Effects of Adolescent Exposure to Nicotine on Adult Behavior

A second aim of this study was to examine whether exposure to nicotine during the adolescent period alters nicotine-related reinforcement enhancement during adulthood. Our results indicate that there was no carryover effect of adolescent nicotine exposure on subsequent adult behavior. This is shown by comparing the rates of VS reinforcement across sessions in the two groups of animals similarly treated with nicotine as adolescents but who

received either saline or nicotine as adults (i.e., NIC(VS)/NIC(VS) group vs. NIC(VS)/SAL(VS) group). The animals continuing to receive nicotine as adults showed significantly higher levels of responding compared to the saline group. The response rates for the nicotine and saline treated adults diverge by the second session (Figure 1B). Moreover, animals who received saline injections as adolescents but nicotine as adults (SAL(VS)/NIC(VS)) reached equivalent levels of responding as the animals that received nicotine during both developmental phases (NIC(VS)/NIC(VS)). Additionally, all animals that received saline injections as adults converged to similar rates of responding. Together, the results of this study indicate that current nicotine exposure, not a previous history of exposure during adolescence, most strongly affects adult responding for the VS. Furthermore, although adult rats receiving nicotine and responding for the VS with a history of VS in adolescence had similarly high rates of responding whether or not they were exposed to nicotine during adolescence, we cannot exclude a ceiling effect masking a significant interaction.

These results extend previous reports examining the effects of adolescent nicotine exposure on subsequent responding in adulthood. For example, Levin et al. (2003) found that female rats that initiated nicotine self-administration during adolescence had higher self-administration rates than rats that began self-administration as adults. In a subsequent study, Levin et al. (2007) tested male rats and also found that adolescent-onset nicotine self-administration rates were increased relative to adult-onset males. However, this effect declined over time and self-administration rates eventually approached adult-onset group levels. The critical distinction between the current study and previous work is that we focused on reinforcement enhancement per se. When viewed in light of the work by Levin et al. (2003; 2007), our findings raise the possibility that adolescent exposure to nicotine alters the primary reinforcing but *not* reinforcement enhancing effect of nicotine in adulthood. It is interesting to note that previous studies using adult rats have demonstrated that the reinforcement enhancing effect of nicotine is pharmacologically dissociable from its primary reinforcing effect (e.g., Palmatier et al., 2009), suggesting different underlying mechanisms that may follow distinct developmental trajectories. The precise neural mechanisms underlying the reinforcement enhancing effect are currently not well understood (c.f., Chaudhri et al., 2006). Future work will be needed to better understand the mechanisms underlying the reinforcement enhancing effect of nicotine during adolescence and whether different neural substrates (e.g., nicotinic receptor subtypes) are involved during adolescence compared to adulthood.

It is interesting to note that animals that responded for the VS as adolescents and received nicotine as adults showed overall higher rates of responding compared to animals who did not respond for the VS as adolescents but were exposed to nicotine while responding for the VS as adults. One possible interpretation of this finding is that previous exposure to, and responding for, the VS in adolescence resulted in it being a stronger reinforcer in adulthood. This outcome is similar to previous studies suggesting that nicotine may have a more pronounced reinforcement enhancing effect on more reinforcing stimuli compared to those with less reinforcing value (Chaudhri et al., 2006; Palmatier et al., 2007; Caggiula et al., 2009). This interpretation is speculative, however, since the current design cannot disentangle VS exposure during adolescence from the total duration of VS exposure. Future work would be needed to examine whether the reinforcing strength of the VS stimulus increased with experience, particularly during adolescence.

4.3 Additional Considerations

Despite the clear conclusions that can be drawn from these data, there were issues not addressed by this study. Adult behavior was examined over a relatively brief duration (9 days) and limited our ability to assess potential consequences of adolescent nicotine exposure that may have emerged after an extended time period. Responding during the FR

and PR sessions may have reached a ceiling that precluded observing group differences in nicotine exposed animals. Also, we examined responding under a FR 2 schedule and it is possible that under different schedules of reinforcement we would see different patterns of results. Additionally, we did not examine conditioned reinforcers. The VS fits the functional definition of an unconditioned reinforcer (Ferster and Skinner, 1957) because it was never associated with a programmed unconditioned reinforcer yet it maintained nose-poking behavior in groups of adolescent and adult rats (cf., saline groups in Figure 1). Others, dating back to at least the 1960's, have described similar unconditioned reinforcing effects of sensory stimuli (Stewart, 1960). Future studies should examine the effects of nicotine on responding for conditioned reinforcers in adolescent animals.

Another set of considerations pertains to the study of adolescent rats. In the present study, the design included receiving rats that were weaned slightly earlier than normal by the supplier (PND20 instead of PND21) and then shipped to our animal facility where they were housed singly under conditions of reversed lighting (lights on at 7:00pm). (They were housed under these conditions for a week prior to the initiation of the experiments on PND28.) In addition, these rats were slightly food restricted during testing. All of these issues may have contributed to stress in these animals, which may have impacted the results. These issues have received some attention in the literature (e.g., Wiley and Evans, 2009), and there is evidence that stress occurring during adolescence alters responses in adolescence and adulthood (Burke et al., 2011; Barha et al., 2011). Thus, it is prudent to minimize potential stressors during the adolescent period. However, it is unlikely that these factors in the experimental design have an impact in the conclusions of this study. Indeed, in a previous study that compared the effects of haloperidol, clozapine, and Δ^9 -tetrahydrocannabinol on adolescent rats that were bred in house compared to those that had been shipped from a supplier (similar to those rats used in the present studies), no qualitative differences were noted (and the quantitative differences were minor) (Wiley and Evans, 2009).

4.4 Summary

The current experiment showed that adolescent rats demonstrate the reinforcement enhancing effects of nicotine. This suggests that the reinforcement enhancing effects of nicotine may be an important component of nicotine self-administration and smoking during adolescence, similar to adulthood. Moreover, we also showed that exposure to nicotine during adolescence does not significantly alter nicotine-related reinforcement enhancement during adulthood. This suggests that the longer term consequences of human adolescent smoking may be better explained by factors other than lasting effects of nicotine on adult sensitivity to non-nicotine reinforcers.

Acknowledgments

Role of funding source: Research made possible by R01 DA010464

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Figure 1.

Mean ($\pm$ SEM) visual stimulus presentations from the Adolescent (A) and Adult (B) phases are presented as a function of session. Sessions depicted occurred following four days of response acquisition, which did not include pre-session nicotine injections (FR1: PND 25, FR2: PND, 26–28). The term before the slash in the key refers to the drug solution during the adolescent phase, the term following the slash refers to the adult phase solution, and the parenthetical “VS” indicates exposure to VS contingencies. All statistical results are reported in the text and sample sizes are reported in Table 1.

Figure 2.

Mean ($\pm$ SEM) break points for all groups during the Adolescent and Adult phases. The title “VS History” refers to groups 1–4 and “No VS History” refers to groups 5–8 (Table 1). In the legend, the term before the slash refers to the drug solution in the adolescent phase and the term following the slash refers to the adult phase solution. Asterisks represent a significant effect of Adolescent Drug ($p<0.001$). Addition symbols represent a significant effect of Adult Drug ($p<0.001$). Pound symbols represent a significant difference between groups with and without an adolescent VS History during the adult phase ($p<0.001$). Sample sizes are reported in Table 1.

Figure 3.

Mean (SEM) visual stimulus presentations from the Adolescent and Adult phases are presented for all groups. The title “VS History” refers to groups 1–4 and “No VS History” refers to groups 5–8 (Table 1). The term before the slash refers to the drug solution during the adolescent phase, the term following the slash refers to the adult phase solution, and parenthetical “VS” indicates exposure to VS contingencies. Asterisks represent a significant effect of Adolescent Drug ($p < 0.001$). Addition symbols represent a significant effect of Adult Drug ($p < 0.001$). Pound symbols represent a significant difference between groups with and without an adolescent VS History during the adult phase ($p < 0.001$). Sample sizes are reported in Table 1.

Table 1

Procedures for all groups

Group	Adolescent Phase		Adult Phase	
	Drug	VS	Drug	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