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Short communication

Effects of nicotine exposure on oral methamphetamine self-administration, extinction, and drug-primed reinstatement in adolescent male and female rats

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ABSTRACT

Background: Adolescent nicotine exposure increases methamphetamine (MA) intake in adult male rats; however, little is known about how nicotine affects MA self-administration during the adolescent period. Therefore, we assessed whether exposing rats to nicotine during early or late adolescence affects oral MA self-administration.
Methods: 146 male and female rats were treated with saline or nicotine (0.16 or 0.64 mg/kg) from postnatal day (PD) 25-PD 34 (the early exposure phase) and/or PD 35-PD 55 (the late exposure phase). Rats began an oral MA self-administration procedure on PD 35.
Results: Only the sex variable, but not nicotine, affected sucrose and MA acquisition, as female rats had more nose pokes than males during training. On the test sessions, female rats exposed to nicotine (0.64 mg/kg) in the early exposure phase had more active nose pokes than saline-treated female rats or nicotine-treated male rats. Rats exposed to nicotine (0.16 mg/kg) in the late exposure phase had fewer active nose pokes during testing than rats exposed to saline. Nose poke responding during extinction was not altered by nicotine exposure, but administering nicotine (0.16 or 0.64 mg/kg) to male rats in the early exposure phase did decrease nose pokes during the drug-primed reinstatement session.
Conclusions: Our results show that adolescent female rats are more sensitive to the reinforcing effects of oral sucrose and MA than adolescent males, and that preadolescent nicotine exposure enhances oral MA self-administration in female rats. These findings suggest that preteen nicotine use may increase vulnerability to later MA abuse in teenage girls.

1. Introduction

Exposing adolescent rodents to nicotine alters responding to a number of addictive drugs if testing occurs in adulthood (Anker and Carroll, 2011; Collins and Izenwasser, 2004; Hutchison and Riley, 2008; McMillen et al., 2005; Pipkin et al., 2014; Santos et al., 2009). Specifically, adolescent nicotine exposure potentiates the reinforcing value of cocaine and alcohol in adult rats (Anker and Carroll, 2011; McMillen et al., 2005; Reed and Izenwasser, 2017), and decreases the aversive properties of cocaine (Hutchison and Riley, 2008). In addition, nicotine administration during adolescence increases the intake of methamphetamine (MA) in adult male rats (Collins and Izenwasser, 2004; Pipkin et al., 2014). In humans, the interaction between nicotine and MA is less clear, but there is evidence that a relationship does exist. For example, cigarette smoking is almost four times more prevalent in MA users than in the general population (Grant et al., 2007; McPherson et al., 2018; Weinberger and Sofuoglu, 2009) and there is a strong correlation between adolescent smoking and later MA use (Brecht et al., 2007; Brensilver et al., 2013; Russell et al., 2008).

Despite evidence from adult human and rodent studies, it is unknown whether adolescent nicotine exposure changes the reinforcing properties of MA prior to adulthood (i.e., during the adolescent period). One reason for this omission is that proportionately fewer human adolescents abuse MA than adults (Johnston et al., 2018), so relatively less research is focused on the adolescent period. Nonetheless, understanding MA use during adolescence is of importance, because

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adolescent MA users have poorer treatment outcomes, and imaging studies show they are more vulnerable to MA-related structural changes (Buck and Siegel, 2015; Kim et al., 2018; Lyoo et al., 2015; Teixeira-Gomes et al., 2015). A second reason why there are relatively few preclinical studies examining the reinforcing value of MA in adolescent rats is that intravenous self-administration, which is the primary method for studying the addictive properties of drugs, is less suitable for the adolescent age group. Specifically, adolescence encompasses a relatively short time-frame in rodents and it is difficult to complete behavioral training, surgery, recovery, and testing within the limits of this ontogenetic period. Thus, in the present investigation we used an oral MA self-administration procedure to assess the effects of nicotine exposure on the reinforcing properties of MA during adolescence.

2. Methods

2.1. Subjects

Subjects were 146 young male and female rats (n = 9–11) of Sprague-Dawley descent (Charles River, Hollister, CA) born and raised at California State University, San Bernardino (CSUSB). Subjects were cared for according to the "Guide for the Care and Use of Mammals in Neuroscience and Behavioral Research" (National Research Council, 2010) under a research protocol approved by the Institutional Animal Care and Use Committee of CSUSB.

2.2. Drugs

(−)-Nicotine hydrogen tartrate and (±)-MA hydrochloride (Sigma-Aldrich, St. Louis, MO) were dissolved in saline. Nicotine injections were administered subcutaneously (SC), whereas MA injections were administered intraperitoneally (IP). Both drugs were dissolved in saline and the pH of the nicotine solution was adjusted to 7.4. Nicotine doses were expressed as the free base. For the drinking solutions, MA and sucrose were dissolved in distilled water.

2.3. In vivo drug treatment

During the early exposure phase, rats were injected with nicotine (0.16 or 0.64 mg/kg) or saline from PD 25-PD 34. During the late exposure phase (starting on PD 35), rats in the 0.16 and 0.64 mg/kg exposure groups either continued to receive the same nicotine dose they received during the early exposure phase or they were switched to saline. Rats that received saline during the early exposure phase were given 0.16 or 0.64 mg/kg nicotine during the late exposure phase or they continued to receive saline injections. Drug treatments starting on PD 35 continued until the end of the experiment. Nicotine doses were chosen based on experiments in adolescent and adult rats, which showed that low doses of nicotine (below 0.2 mg/kg) were equally rewarding to adult and adolescent rats; whereas, higher doses of nicotine (over 0.4 mg/kg) were more rewarding to adolescent rats than adults (Torres et al., 2008). In summary, there were seven drug groups (early exposure/late exposure): SAL/SAL, 0.16 N/0.16 N, 0.16 N/SAL, SAL/0.16 N, 0.64 N/0.64 N, 0.64 N/SAL, SAL/0.64 N (N = nicotine).

2.4. Apparatus

MA self-administration occurred in standard operant chambers (Coulbourn Instruments, Whitehall, PA). Each chamber contained two nose poke operandums (2 cm from the floor), an optical lickometer, a house light, a stimulus light, and a sound cue (500 Hz, 10 dB above background). The two nose poke operanda were positioned on the front wall of the chamber, with the optical lickometer positioned between them. The stimulus light and sound cue were located directly above the active nose poke hole. The house light was located on the rear wall of the chamber and, except for 20 s timeout periods, the house light remained on while rats were inside the operant chamber. Each chamber was housed in a soundproof isolation cubicle and controlled by an IBM compatible computer interfaced with a data collection program (Graphic State, Coulbourn Instruments).

2.5. Nose poke training

Starting on PD 33, rats were pre-exposed to a 10 % sucrose solution for 32 h in their home cage. On PD 35, rats were placed in a self-administration chamber and allowed to nose poke for access to a 10 % sucrose (w/v) solution on an FR1 schedule for 1 h each day until criterion was met (≥ 10 presentations for 2 consecutive days). Nose poke responses in the active hole resulted in the presentation of a stimulus light, sound cue, and a 30 s presentation of a liquid dropper. After each liquid dropper presentation, the active nose poke hole became inactive for 20 s, which was indicated by the absence of the house light. Following each self-administration session, rats were injected with nicotine (0.16 or 0.64 mg/kg) or saline in their home cage. On training days, water availability was restricted for 16 h/day to accelerate acquisition of operant responding. Following nose poke training, rats were food restricted to 90 % of their free-feeding weight for the remainder of the experiment, while water was made available ad-libitum. Rats that failed to meet the training criterion were excluded from the study.

2.6. Self-administration procedure: acquisition

Once the sucrose-training criterion was met, MA fade-in and sucrose fade-out was carried out across seven stages, with nose pokes in the active hole resulting in the same consequences as during nose poke training. In stage 1, a 10 % sucrose solution was presented alone. In stage 2, a low dose of MA (20 mg/l) was introduced into an 8.5 % sucrose solution. In stages 3–6, a high dose of MA (40 mg/l) was introduced into the sucrose solutions (i.e., 6.5 % for stage 3, 4.5 % for stage 4, 2.5 % for stage 5, and 0.5 % for stage 6). In stage 7, no sucrose was present in the MA (40 mg/l) liquid solution.

During stages 1–2, liquid solutions were presented on an FR1 schedule; during stages 3–7, liquid solutions were presented on an FR2 schedule. The criterion for stages 1–6 was ≥ 10 presentations for each 2 h session. Stage 3 required an additional criterion of ≥ 10 presentations for 2 consecutive days. Rats were exposed to stage 7 for three consecutive days. If rats did not meet criteria for a particular stage then they remained on that stage for at least 4 days, after which they were advanced to the next stage.

2.7. Self-administration procedure: extinction

Extinction training began following MA (40 mg/l) acquisition. During extinction, rats underwent 2 h training sessions, in which nose poke behavior resulted in no scheduled consequences, but responses were recorded. Rats remained in extinction for 7 consecutive days or until active nose poke responses were < 10 % of the last day of FR2 MA (40 mg/l) acquisition for two consecutive days.

2.8. Self-administration procedure: drug-primed reinstatement

Once extinction criteria were met, all rats were given a priming injection of MA (1 mg/kg, IP) 5 min before being placed in the self-administration chambers. Reinstatement sessions lasted 2 h, during which nose pokes resulted in no consequences.

2.9. Data analysis

Data from rats exposed to low- and high-dose nicotine were initially analyzed separately. Total nose pokes and amount of sucrose or drug solution consumed during sucrose training, stage 7 acquisition testing

(MA-only sessions), and drug-primed reinstatement were analyzed using 2 × 2 × 2 (sex × early exposure × late exposure) ANOVAs. Total nose pokes, drug solution consumed, and days to criterion during stages 1–6 of acquisition (i.e., the training phase) were analyzed by 2 × 2 × 2 × 6 (sex × early exposure × late exposure × stage) repeated measures ANOVAs. Extinction nose pokes were analyzed using 2 × 2 × 2 × 7 (sex × early exposure × late exposure × days) repeated measures ANOVAs. To examine the effects of dose, data were analyzed according to treatment group. Specifically, stages 1–6 of acquisition were analyzed by 2 × 7 × 6 (sex × treatment × stage) repeated measures ANOVAs; whereas, sucrose training, stage 7 acquisition testing (MA-only sessions), and drug-primed reinstatement were analyzed using 2 × 7 (sex × treatment) ANOVAs. Extinction nose pokes were analyzed using 2 × 7 × 7 (sex × treatment × days) repeated measures ANOVAs. Effect sizes were reported as partial eta squared (η_p^2) and categorized based on the following scale: $\eta_p^2 \leq 0.03$ (small effect), $\eta_p^2 > 0.03$ and ≤ 0.10 (medium effect), and $\eta_p^2 > 0.10$ (large effect) (Labots et al., 2016). When the assumption of sphericity was violated, the Huynh-Feldt statistic was used to adjust degrees of freedom. Corrected degrees of freedom were rounded to the nearest whole number and italicized. Post-hoc comparisons were made with Tukey tests, $p < 0.05$. All analyses were done using IBM SPSS Statistics, version 26 (IBM Corporation, Armonk, NY).

3. Results

3.1. Body weight

Body weights increased significantly from PD 25 (day of first nicotine injection) until PD 54 (earliest completion day for the experimental protocol) [day main effect, $F_{(3, 341)} = 1436.522$, $p = 0.001$, $\eta_p^2 = 0.914$ (see supplemental Table 1)]. Male rats were heavier than female rats on each day tested [sex × day interaction, $F_{(3, 341)} = 52.091$, $p = 0.001$, $\eta_p^2 = 0.278$]. Nicotine treatment did not alter body weight of male or female rats.

3.2. Sucrose training

Neither nose pokes, sucrose solution consumed, or days to criterion were altered by early (i.e., PD 25 to PD 34) or late exposure (starting PD 35) to 0.16 mg/kg nicotine (see supplemental Tables 2 and 3). Early exposure to 0.64 mg/kg nicotine also did not alter active nose pokes, sucrose solution consumed, or days to criterion. Early nicotine (0.64 mg/kg) exposure did decrease inactive nose pokes, but this decrease was only evident in male rats [sex × early exposure interaction, $F_{(1, 73)} = 6.651$, $p = 0.012$, $\eta_p^2 = 0.083$]. Late exposure to 0.64 mg/kg nicotine had no effect on active nose pokes, amount of sucrose consumed, or days to criterion, but the drug did increase inactive nose pokes in male rats [sex × late exposure interaction, $F_{(1, 73)} = 6.798$, $p = 0.011$, $\eta_p^2 = 0.085$]. Separate analyses showed that the low and high doses of nicotine did not differentially affect performance during sucrose training, but female rats consumed less sucrose solution than male rats [sex main effect, $F_{(1, 129)} = 7.835$, $p = 0.006$, $\eta_p^2 = 0.057$, see Fig. 1, lower graph].

3.3. Acquisition of MA self-administration—training phase

During the six training stages, neither early or late nicotine exposure altered active nose pokes, inactive nose pokes, sucrose/MA solution consumed, or days to criterion (see supplemental Tables 2 and 3). Female rats evidenced a greater number of active and inactive nose pokes and consumed less of the sucrose/MA solution than male rats [sex main effects, $F_{(1, 129)} = 4.672$, $p = 0.033$, $\eta_p^2 = 0.035$; $F_{(1, 129)} = 7.530$, $p = 0.007$, $\eta_p^2 = 0.057$; $F_{(1, 129)} = 11.906$, $p = 0.001$, $\eta_p^2 = 0.084$, respectively (see Fig. 1)].

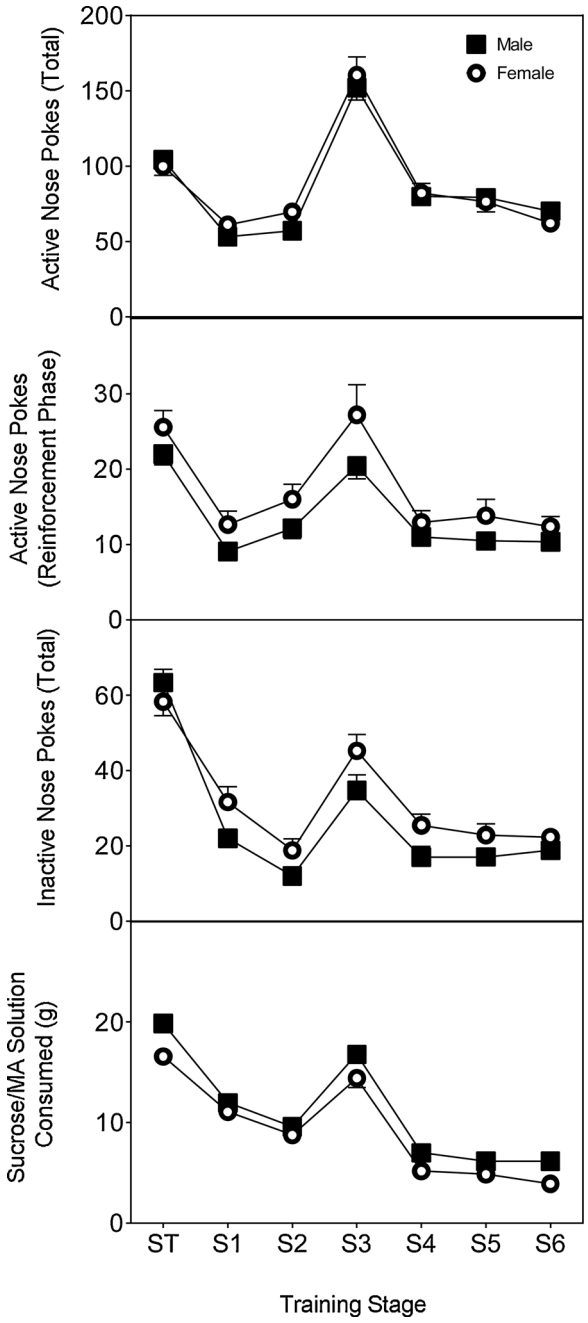

Fig. 1. Mean (± SEM) active nose pokes, active nose pokes during the reinforcement phase, inactive nose pokes, and sucrose/MA solution consumed. Adolescent male ($n = 73$) and female ($n = 70$) rats were exposed to saline or nicotine (0.16 or 0.64 mg/kg) from PD 25-PD 34 (early exposure phase) and then treated with saline or nicotine (0.16 or 0.64 mg/kg) from PD 35 until the end of testing (late exposure phase). ST = sucrose training and S1-S6 = stages 1-6.

3.4. Acquisition of MA self-administration—test sessions

During the MA-only self-administration sessions (i.e., stage 7), nose pokes varied according to treatment and sex. Administering nicotine (0.16 mg/kg) during the early exposure phase decreased inactive nose pokes [early exposure main effect, $F_{(1,75)} = 5.217$, $p = 0.025$, $\eta_p^2 = 0.065$ (see Table 1)]. In contrast, treating rats with the high dose of nicotine (0.64 mg/kg) during the early exposure phase increased active nose pokes, but this effect was only significant in female rats [sex × early exposure interaction, $F_{(1,73)} = 4.703$, $p = 0.033$, $\eta_p^2 = 0.061$,

Table 1
Acquisition data from rats in the MA only stage (i.e., Stage 7). Rats were treated with saline or nicotine (0.16 or 0.64 mg/kg) from PD 25-PD 34 (early exposure phase) and then conditioned with saline or nicotine (0.16 or 0.64 mg/kg) from PD 35 to the end of the experiment (late exposure phase).

Group	ANP	ANP-R	ANP-TO	INP	INP-TO	SC
SAL-SAL						
Males	84.88 (12.37)	16.11 (2.09)	8.22 (1.92)	35.22 (12.36)	5.22 (1.28)	9.30 (1.14)
Females	131.33 (32.41)	22.44 (6.88)	14.33 (5.86)	53.44 (10.89)	7.89 (2.88)	10.79 (1.41)
SAL-0.16N						
Males	87.30 (16.92)	14.00 (4.14)†	6.03 (1.56)	47.40 (17.37)	5.50 (2.74)	8.18 (1.08)
Females	88.45 (8.77)	16.81 (3.24)†	8.09 (1.89)	49.48 (13.05)	3.55 (0.94)	8.08 (1.00)
0.16N-SAL						
Males	80.09 (13.97)	14.54 (3.74)	4.09 (1.08)	19.72 (3.43)*	2.27 (0.57)	8.87 (1.09)
Females	88.70 (9.59)	22.30 (4.27)	12.10 (1.98)	35.70 (5.72)*	3.50 (0.98)	11.82 (1.90)
0.16N-0.16N						
Males	67.18 (11.59)	8.27 (1.79)†	4.18 (1.00)	18.18 (4.88)*	2.09 (0.99)	8.73 (1.43)
Females	100.55 (24.46)	16.22 (5.61)†	10.77 (3.93)	42.00 (11.95)*	6.00 (3.56)	7.13 (1.51)
SAL-0.64N						
Males	124.72 (31.12)	21.54 (6.06)	7.63 (1.91)	43.81 (10.75)	4.90 (1.31)	9.30 (1.13)
Females	149.80 (42.74)	18.10 (3.62)	25.50 (18.12)	46.00 (6.35)	7.20 (3.40)	9.43 (1.60)
0.64N-SAL						
Males	92.70 (23.00)	12.80 (4.45)	7.30 (2.96)	27.10 (6.12)	1.80 (0.41)	10.17 (1.94)
Females	181.72 (54.25)	38.09 (8.53)**	32.09 (25.27)	42.18 (6.45)	7.09 (2.42)	10.70 (0.91)
0.64N-0.64N						
Males	112.81 (17.08)	16.00 (3.72)	6.63 (1.44)	34.00 (8.61)	3.63 (1.10)	9.30 (1.18)
Females	138.60 (21.76)	29.10 (6.93)**	12.30 (4.17)	51.70 (11.38)	5.40 (1.29)	8.96 (1.43)

ANP = total active nose pokes, ANP-R = total active nose pokes during the reinforcement phase, ANP-TO = total active nose pokes during the time out phase, INP = total inactive nose pokes, INP-TO= total inactive nose pokes during the time out phase, SC = MA solution consumed, (SEM). *indicates a difference from rats exposed to saline during the early exposure phase (before PD 35); **indicates a difference from same-sex rats treated with saline during the early exposure phase, †indicates a difference from rats given saline during the late exposure phase (after PD 34), $p < 0.05$.

Tukey tests, $p < 0.05$ (see Fig. 2 and Table 1)]. The amount of sucrose/MA solution consumed and the number of nose pokes during time-out were unaffected by nicotine.

Exposure to 0.16 mg/kg nicotine after PD 34 (i.e., the late exposure phase) decreased active nose pokes during the reinforcement period [late exposure main effect, $F_{(1, 75)} = 4.090$, $p = 0.047$, $\eta_p^2 = 0.052$; see Fig. 2 and Table 1]. Moreover, rats treated with 0.16 mg/kg nicotine during the late exposure phase consumed less MA solution than rats treated with saline [late exposure main effect, $F_{(1, 75)} = 5.217$, $p = 0.025$, $\eta_p^2 = 0.065$]. Late exposure to nicotine did not alter inactive nose pokes or active nose pokes during the time-out phase. Regardless of the nose poke measures being assessed (e.g., total active nose pokes, active nose pokes during timeout, active nose pokes during the reinforcement phase, total inactive nose pokes, inactive nose pokes during timeout), female rats had a greater number of nose pokes than male rats [sex main effects, $F_{(1, 129)} = 5.235$, $p = 0.024$, $\eta_p^2 = 0.039$; $F_{(1, 129)} = 4.350$, $p = 0.039$, $\eta_p^2 = 0.033$; $F_{(1, 129)} = 10.100$, $p = 0.002$, $\eta_p^2 = 0.073$; $F_{(1, 129)} = 6.630$, $p = 0.011$, $\eta_p^2 = 0.049$; $F_{(1, 129)} = 5.183$, $p = 0.024$, $\eta_p^2 = 0.039$; respectively]. Sex did not affect the amount of MA solution consumed.

3.5. Extinction training and drug-primed reinstatement

Active nose pokes decreased across the seven extinction days [day main effect, $F_{(5, 693)} = 17.797$, $p = 0.001$, $\eta_p^2 = 0.124$, see supplemental Tables 4 and 5]. Early or late nicotine exposure did not alter active nose pokes during extinction, but early exposure to 0.16 mg/kg nicotine did decrease inactive nose pokes during extinction [early exposure main effect, $F_{(1,71)} = 5.933$, $p = 0.017$, $\eta_p^2 = 0.077$]. Similar to the acquisition phase, female rats had more active nose pokes than male rats [sex main effect, $F_{(1, 126)} = 5.675$, $p = 0.019$; $\eta_p^2 = 0.043$].

On the drug-primed reinstatement day, rats in the 0.16 N/SALl and 0.64 N/SAL groups had fewer active nose pokes than saline controls (i.e., the SAL/SAL group); however, this effect was only evident in male rats [sex × treatment interaction, $F_{(6, 126)} = 2.594$, $p = 0.021$; $\eta_p^2 = 0.109$, Tukey tests, $p < 0.05$]. Inactive nose pokes of male rats were also reduced by early exposure to nicotine (0.16 mg/kg and 0.64 mg/kg) [sex × early exposure interaction, $F_{(1, 71)} = 5.334$, $p = 0.024$; $\eta_p^2 = 0.070$; $F_{(1, 71)} = 4.606$, $p = 0.035$; $\eta_p^2 = 0.060$, respectively].

4. Discussion

In the current study, exposing rats to nicotine during early adolescence (PD 25-PD 34) increased MA-rewarded responding during late adolescence. These results are consistent with many studies showing that adolescent nicotine exposure alters drug responsivity in adulthood (Alajaji et al., 2016; Anker and Carroll, 2011; McMillen et al., 2005; Pipkin et al., 2014; Reed and Izenwasser, 2017). Curiously, nicotine exposure did not alter responding for sucrose or the mixed sucrose/MA solution (i.e., nicotine only affected responding for the MA solution). This finding is in agreement with studies showing that pre-exposure to nicotine does not alter responding for sucrose pellets or a mixed sucrose/alcohol solution (Randall et al., 2019; Schwartz et al., 2018). Nicotine exposure produced a different pattern of MA-rewarded responding depending on the dose of nicotine administered. Specifically, exposure to a low dose of nicotine (0.16 mg/kg) starting on PD 35 (i.e., the late exposure phase) decreased MA-rewarded responding, while exposing female rats to 0.64 mg/kg nicotine on PD 25-PD 34 (i.e., the early exposure phase) increased MA-rewarded responding. During extinction, only inactive nose pokes were altered by nicotine treatment, because early exposure to 0.16 mg/kg nicotine decreased inactive nose pokes. Early exposure to nicotine also decreased active and inactive nose pokes after a drug prime, but this nicotine-mediated reinstatement effect was only significant in male rats.

The pattern of current results was not fully anticipated because we previously reported that exposing adolescent rats to 0.16 mg/kg nicotine on PD 35-PD 50 increased adult MA-rewarded responding on an intrajugular self-administration task, while a higher dose of nicotine (0.64 mg/kg) did not alter MA-rewarded responses (Pipkin et al., 2014). In the present study, exposing adolescent rats to 0.16 mg/kg nicotine on PD 35-PD 55 decreased MA-rewarded responding on an oral self-administration task, while 0.64 mg/kg nicotine increased MA-rewarded responding. The reasons for these discrepancies are unknown; however, age of the rats and/or differences in methodology (i.e., intrajugular vs.

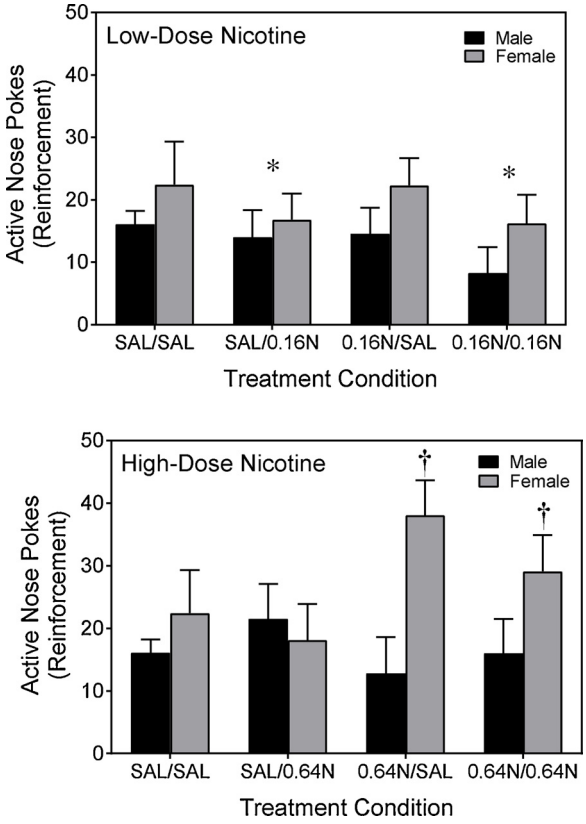

Fig. 2. Mean (± SEM) active nose pokes during the reinforcement phase. Adolescent male and female rats (n = 9-11) were exposed to saline or nicotine from PD 25-PD 34 (early exposure phase) and then exposed to saline or nicotine from PD 35 until the end of testing (late exposure phase). Low-dose nicotine groups are shown in the upper graph, while high-dose nicotine groups are shown in the lower graph. *Indicates a significant difference from male and female rats exposed to saline during the late exposure phase (late exposure main effect, $p < 0.05$). †Indicates a significant difference from same-sex rats exposed to saline during the early exposure phase (sex × early exposure condition interaction, $p < 0.05$).

oral self-administration) are likely to be involved. Most notably, it is possible that the reinforcing value of oral MA differs from intravenously administered MA; thus, these two experimental paradigms may be differentially sensitive to nicotine dose effects. While several studies have demonstrated that the rewarding properties of MA can be assessed using a two-bottle choice procedure (Alavijeh et al., 2019; Doyle et al., 2015; Hajheidari et al., 2015), few studies have utilized oral MA self-administration in rodents, and all have been conducted using mice (Fultz et al., 2017; Shabani et al., 2012; Szumlinski et al., 2017).

Alternatively, age at the beginning of nicotine exposure may explain the differences between our current study and Pipkin et al. (2014). Many of nicotine's effects vary according to the developmental stage in which drug exposure occurred (i.e., early adolescence, late adolescence, or adulthood). For example, acute nicotine-induced locomotor activity, nicotine-induced conditioned place preference, nicotine-induced accumbal dopamine release, and nicotine-induced acetylcholine receptor upregulation all differ depending on the age at which nicotine exposure began (Belluzzi et al., 2004; Corongiu et al., 2020; Hoegberg et al., 2015). Age-dependent differences in nicotine sensitivity are also consistent with findings from the alcohol literature, because mid-adolescent alcohol exposure produces very different behavioral effects than late adolescent exposure (for review, see Spear, 2015). Thus, it is not surprising that starting the nicotine regimen on PD 25 (present study), rather than PD 35 (Pipkin et al., 2014), would modify the impact of nicotine treatment on MA intake.

While several studies have demonstrated that pretreatment with nicotine can enhance the response to psychostimulant treatment (Alajaji et al., 2016; Anker and Carroll, 2011), the mechanism responsible for this nicotine-induced change is unknown. One possibility is that enhanced responsiveness is due to nicotine potentiating cholinergic activity. Specifically, repeated nicotine exposure causes an upregulation of nicotinic receptors (Hernandez and Terry, 2005), which may sensitize the VTA to later MA-induced acetylcholine release (Dobbs and Mark, 2008). Another possibility is that nicotine increased the number of MA-reinforced nose pokes by affecting 5-HT1A receptor systems. Evidence for this explanation is two-fold, as (a) repeated nicotine exposure during adolescence increases 5-HT1A receptor binding in the limbic system, and (b) treatment with the 5-HT1A antagonist WAY 100,635 blocks the nicotine-induced enhancement of cocaine self-administration (Dao et al., 2011). The possibility of 5-HT1A involvement is particularly intriguing, because nicotine-induced changes in 5-HT1A receptor binding only occurred when nicotine was administered during early adolescence (i.e., as with our treatment protocol). It is unknown why only female rats showed enhanced responding for MA after early nicotine (0.64 mg/kg) exposure; however, Pomfrey et al. (2015) reported that nicotine (0.6 mg/kg) does not affect cocaine self-administration in male rats.

Late nicotine exposure (PD 35-PD 55) produced a different pattern of effects than early nicotine exposure (PD 25-PD 34). In general, we found that exposure to nicotine after PD 34 reduced MA-induced nose pokes, while exposure to nicotine on PD 25-PD 34 had no effect on active nose pokes. These results could be interpreted as providing evidence of nicotine either decreasing or increasing the reinforcing value of MA. Specifically, (a) nicotine may increase the rewarding value of MA, thus rats require less MA for the same reinforcing effect, or (b) nicotine may devalue MA, thus making it a less preferred reward. Unfortunately, very few preclinical studies have assessed the important issue of concurrent use of nicotine and MA. Further studies will be necessary to delineate the effects of concurrent nicotine use on drug reward.

Lastly, multiple sex effects were in evidence, as female rats consistently responded at a higher rate than male rats during MA self-administration and extinction testing. This finding is in agreement with other preclinical studies showing that female rats acquire MA self-administration more rapidly and exhibit a more robust drug-primed reinstatement than male rats (Kucerova et al., 2009; Reichel et al., 2012; Roth and Carroll, 2004; Ruda-Kucerova et al., 2015). Moreover, when compared to human male MA users, females report MA initiation at a younger age, they show a more rapid increase in the frequency of MA use, and females bear a greater psychological burden regarding MA use (Dluzen and Liu, 2008; Liu et al., 2013; Rawson et al., 2005; Simpson et al., 2016).

In summary, we found that: (a) early and late adolescent nicotine exposure differentially affected MA self-administration, and (b) female rats, when compared to male rats, consistently responded at a higher rate for access to MA. These results show that oral self-administration can be used to measure drug reward in rats. Importantly, this procedure allows for the direct assessment of drug reward during the comparatively short adolescent period.

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Contributors

Z.R. Harmony and C.A. Crawford designed the study. Z.R. Harmony, E.M. Alderson, I. Garcia-Carachure, L.D. Bituin conducted the

experiment. Z.R. Harmony did the initial statistical analyses and wrote the first draft of the manuscript. C.A. Crawford assisted with the statistical analyses and edited the manuscript prior to submission. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors have no relevant conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2020.107927.

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