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Nicotine exposure beginning in adolescence enhances the acquisition of methamphetamine self-administration, but not methamphetamine-primed reinstatement in male rats

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Abstract

Background—Nicotine is commonly abused in adolescence and is believed to be a “gateway” to other drugs of abuse [e.g., methamphetamine (METH)]. The relationship between early nicotine exposure and later METH use is complicated because the majority of juvenile smokers continue to use cigarettes into adulthood. Thus, the present investigation examined the individual and combined contribution of adolescent and adult nicotine exposure on METH self administration.

Methods—Forty-three male rats were pretreated with saline or nicotine (0.16 or 0.64 mg/kg, SC) from postnatal day (PD) 35–50. On PD 51, subjects were split into the following groups: 0.16/0.16, 0.16/SAL, 0.64/0.64, and 0.64/SAL. Rats were then trained to lever press for METH (0.05 mg/kg) for seven days on an FR1 and seven days on an FR3 reinforcement schedule. After acquisition training, rats underwent 14 days of extinction and were then tested for METH-induced primed reinstatement (1.0 mg/kg, IP).

Results—Data showed that rats receiving continuous injections of the low dose of nicotine (0.16/0.16) obtained more METH infusions versus the control group (SAL/SAL) on an FR1 and FR3 schedule. In addition, rats on the FR3 schedule that received a low dose of nicotine during the adolescent period only (0.16/SAL) had more METH intake than the control group (SAL/SAL).

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Contributors

J.A. Pipkin, A.R. Zavala, and C.A. Crawford designed the study. J.A. Pipkin, G.J. Kaplan, C.P. Plant, S.E. Bain, and S.M. Gill conducted the experiment. J.A. Pipkin did the initial statistical analyses and wrote the first draft of the manuscript. C.A. Crawford assisted with the statistical analyses. A.R. Zavala and C.A. Crawford edited the manuscript prior to submission. All authors contributed to and have approved the final manuscript.

Conflict of Interest

The authors have no relevant conflicts of interest to disclose.

Interestingly, the high dose of nicotine exposure had no effect on METH intake and neither nicotine dose altered METH seeking behavior.

Conclusions—Low dose exposure to nicotine during adolescence enhances the reinforcing effects of METH, while heavier exposure has no effect on METH intake.

Keywords

nicotine; adolescence; methamphetamine; self-administration.

1. INTRODUCTION

Smoking in adolescence is very common (Gilpin et al., 1999) and has been suggested as a potential “gateway” to illicit drug use (for review, see Benowitz, 1999; DiFranza et al., 2000). For example, adolescent nicotine use is strongly associated with later adult methamphetamine (METH) abuse in humans (Brensilver et al., 2013; Russell et al., 2008), and rodent studies have shown that nicotine exposure during adolescence leads to an increased sensitivity to amphetamine and cocaine in adult rats (Collins and Izenwasser, 2004; Santos et al., 2009).

However, the nature of the relationship between adolescent nicotine exposure and the abuse of other drugs is difficult to determine because approximately 80% of adolescent onset smokers continue to smoke into adulthood (Lenny and Enderby, 2008; Warren et al., 2008). Thus, in humans, the effects of adolescent nicotine exposure are usually confounded by continued adult use. Consequently, the combined effects of adolescent and adult nicotine exposure may differ significantly from adolescent alone exposure. Therefore, the purpose of the present investigation was to determine the role of adolescent or combined adolescent and adult nicotine exposure on the acquisition of METH self-administration in adult male rats. In addition, we also investigated the individual and combined roles of adolescent and adult nicotine exposure on METH-induced primed reinstatement of extinguished METH-seeking.

2. Methods

2.1 Subjects

Subjects consisted of 43 male rats of Sprague Dawley descent from seven litters (Charles River Laboratories, 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 Laboratory Animals” (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 (±)-methamphetamine hydrochloride were obtained from Sigma (St. Louis, MO). Both drugs were dissolved in saline (VEH) and the pH of the nicotine solutions was adjusted to 7.4. Nicotine doses were expressed as the free base and were injected subcutaneously (SC). The METH dose was expressed as a salt and was injected intraperitoneally (IP) at a volume of 1.0 ml/kg. For self-administration, METH was administered intravenously (IV) using a syringe pump at a volume of 0.1 ml/infusion.

2.3 In Vivo Drug Treatment

Starting on PD 35, rats were injected with saline or nicotine (0.16 or 0.64 mg/kg, SC) once daily for 16 consecutive days until PD 50. On PD 51, rats were either switched to saline or continued to receive the same nicotine dose they received as adolescents, and these injections continued through extinction training. Thus, there were five groups: SAL/SAL, 0.16/0.16, 0.16/SAL, 0.64/0.64, and 0.64/SAL. Because we were only interested in adolescent onset nicotine use we did not have a SAL/0.16 or SAL/0.64 group. Each animal in the litter was randomly assigned to receive one of the five pretreatment groups at the start of the experiment. Drugs were coded so experimenters were blind to drug group.

2.4 Apparatus

Lever training and METH self-administration was done in standard operant chambers (Coulbourn Instruments, Whitehall, PA). Each chamber contained two stainless steel levers (2 cm from the floor), a house light, a stimulus light, and a sound cue (500 Hz, 10 dB above background). Jugular catheters were connected to liquid swivels (Instech, Plymouth Meeting, PA) via PE-20 tubing. The tubing was encased in a steel spring leash (Plastics One) to prevent damage from the rats. A 20-ml syringe infusion pump (Razel, model A-99; St. Albans, VT) was mounted outside each operant chamber and was connected to the liquid swivels via Tygon tubing. Each chamber was housed in soundproof isolation cubicles and controlled by an IBM compatible computer interfaced with a data collection program (Graphic State, Coulbourn Instruments).

2.5 Lever press training

On PD 55, rats were trained to press a lever for a sucrose pellet on a fixed ratio (FR) 1 until reaching criterion (i.e., at least 10 sucrose pellets earned for two consecutive days). Once rats reached criterion, indwelling jugular catheters were surgically implanted as described below.

2.6 Surgery

To prevent bronchial secretions and ease respiration rats were pretreated with atropine sulfate (10 mg/kg, IP). Five minutes later, rats were anesthetized with a ketamine/xylazine solution (80:6 mg/kg, IP), and if necessary, 2–3% isoflourane gas anesthesia was used to complete the surgery. A silastic catheter connected to a bent 22 gauge metal cannula (Plastics One, Roanoke, VA) was inserted into a small incision in the jugular vein and secured with sterile silk sutures. The wound was then treated with 0.2 ml gentamycin and closed with nylon sutures. The metal end of the catheter was ran subcutaneously along the neck and exited through an incision across the skull and secured to the top of the skull using dental acrylic cement and small anchor screws drilled into the skull. After surgery, rats were treated with ketoprofen (2.0 mg/kg, IP) to control pain. Catheter patency throughout the experiment was maintained by daily flushing with 0.1 ml bacteriostatic saline containing heparin sodium (70 USP U/ml, IV) and ticarcillin disodium (20 mg/ml, IV). For the first five days after surgery, streptokinase (0.67 mg/ml, IV) was also administered.

2.7 Self-Administration Procedure: Acquisition

METH acquisition training (0.05 mg/kg, IV) occurred across two weeks, with a minimum of one week on a FR1 schedule and one week on a FR3 schedule. In each 2 h session, lever presses on the active lever resulted in the simultaneous presentation of a stimulus light and a sound cue (500 Hz, 10 dB above background) followed, one second later, by a 4 s METH infusion. After each infusion, the active lever became inactive for 20 seconds, which was indicated by the absence of the house light. To progress from the FR1 to the FR3 rats had to meet the criterion of receiving 10 infusions for at least two consecutive days.

2.8 Self-Administration Procedure: Extinction

Extinction training started the day after acquisition ended. During extinction training, rats continued to receive daily 2 h training sessions, but lever presses had no scheduled consequences. Rats remained on extinction until active lever responses were below 10% of the last day of FR3 acquisition for two consecutive days.

2.9 Self-Administration Procedure Reinstatement

Following extinction training, subjects were primed with METH (1.0 mg/kg, IP) 5 min before being placed in the chambers. Reinstatement sessions lasted two hours during which lever presses had no consequences.

2.10 Data Analysis

All data from acquisition, extinction, and reinstatement sessions were analyzed by separate one way ANOVAs, with group as the independent variable. Tukey's tests were used to make post hoc comparisons ($p < 0.05$). Data from the acquisition and extinction sessions were collapsed over days as no group differences were noted.

3. RESULTS

3.1 Acquisition of METH Self-Administration (Fixed Ratio Training)

3.1.1 FR1—Rats that received nicotine during both the pre-exposure and continuation periods (0.16–0.16) had significantly more METH infusions in comparison to the saline control group (SAL-SAL) on the FR1 schedule [$F(4,38) = 2.95$, $p < 0.05$, respectively, and Tukey tests, $p < 0.05$] (see Fig. 1). No other group differed from control, but the rats receiving the high dose of nicotine during adolescence and adulthood earned fewer infusions than the 0.16–0.16 group [Tukey tests, $p < 0.05$].

3.1.2 FR3—When switched to the FR3 schedule, rats that received the low dose of nicotine (0.16 mg/kg) during the adolescent pre-exposure period obtained more METH infusions than saline controls regardless of adulthood treatment (see Fig 2). Specifically, rats in the 0.16-SAL and 0.16–0.16 groups earned more METH infusions than the SAL-SAL group [$t(42) = 6.87$, $p < 0.05$; $F(4,38) = 6.10$, $p < 0.001$, Tukey tests, $p < 0.05$, respectively]. Rats that received the high dose of nicotine (0.64-SAL and 0.64–0.64) did not differ from saline treated controls, but both groups did receive fewer METH infusions as compared to rats in the 0.16–0.16 group [Tukey test, $p < 0.05$].

3.2 Extinction Training and Prime Reinstatement

By day 14, most rats had reached the extinction criteria (i.e., 10% of active presses on the last day of FR3 training), and lever presses declined significantly from day 1 to day 14 (data not shown). Treatment with nicotine did not alter lever presses during extinction training. Reexposure to METH (drug prime) reinstated drug-seeking behavior, but this increase was not modified by nicotine treatment (data not shown).

4. DISCUSSION

Previous human and animal studies have demonstrated that adolescent nicotine exposure is correlated with greater drug intake later in life (Brensilver et al., 2013; Russell et al., 2008). The present study found that adolescent nicotine exposure in rats increased METH sensitivity similar to previous rodent investigations using cocaine and METH (Collins and Izenwasser, 2004; Santos et al., 2009; Suemaru et al. 1993). Our data also revealed that while there was a trend for combined adolescent/adult exposure to enhance METH intake more than adolescent exposure alone, there were no significant differences between these treatment groups. Interestingly, the results from our drug reinstatement procedure, however, did not indicate that nicotine exposure increased METH seeking behavior. Specifically, we found that a METH priming injection reinstated drug-seeking behavior to the same degree in rats that had been exposed to saline or nicotine. This finding was consistent with a previous investigation in which nicotine pre-exposure was only given during adulthood (Neugebauer et al., 2010), but in contrast to investigations showing that adolescent nicotine treatment enhanced cocaine-seeking behavior. Curiously, in the Neugebauer et al. (2010) study, a nicotine priming injection was found to enhance METH seeking behavior, but only in rats that were pre exposed to nicotine. This suggests that pre exposure to nicotine may be more problematic than exposure to METH for relapse prevention.

The mechanism for nicotine's ability to enhance METH intake is unknown; however, considering the close interaction between the dopaminergic and cholinergic systems (Mattsson et al., 2004; Wonnacott et al., 2005), the ability of a low dose of nicotine to potentiate the reinforcing properties of METH is not surprising. For example, nicotine has a direct facilitating effect on DA neurons within the VTA (Pidoplichko et al., 1997) and may act directly on the VTA to increase DA release within the nucleus accumbens. METH administration may add to these biological effects (Nakagawa et al., 2011), which may explain how this low dose potentiated the effects of METH.

Surprisingly, we found that nicotine's effect on later METH intake was dose dependent. Specifically, while the low dose of nicotine (0.16 mg/kg) potentiated the reinforcing value of METH treatment, the higher dose (0.64 mg/kg) did not alter the number of METH infusions earned. The precise mechanism for this dose effect is unknown, but it is likely that the effects of nicotine on METH self-administration are biphasic, such that low doses enhance while higher doses reduce the number of infusions. Consistent with this view, there is evidence for a biphasic relationship between nicotine and METH effects. For instance, administration of a low dose of METH enhances nicotine self-administration, while higher doses reduced the number of nicotine infusions (Rauhut et al, 2003). Although the present study did not demonstrate that the 0.64 mg/kg dose of nicotine reduced the number of

METH infusions, higher doses would likely have this effect. Further research using additional doses of nicotine on METH self-administration are necessary to reveal this biphasic effect. In agreement with the notion that a reduction in METH infusions after systemic administration of nicotine represents an enhancement of METH effects, systemic administration of increasing doses of METH reduces rates of responding and METH infusions in a self-administration paradigm (Pickens et al., 1968), akin to decreases in responding and infusions earned with increasing doses of METH in a self-administration paradigm (Aarde et al., 2013; Kitamura et al., 2006).

In summary, the data from the present investigation show that adolescent exposure to a low dose of nicotine, either with or without continued adult exposure, resulted in higher METH intake compared to saline-exposed rats. This finding implies that clinical treatments aimed at preventing METH relapse should also consider the management of nicotine consumption (e.g., tobacco use), as nicotine may enhance the effects of METH. Additionally, these data suggest that nicotine use may be an important contributor to the abuse of METH, and that METH rehabilitation programs should also assess nicotine use in designing treatment plans. Lastly, novel pharmacotherapies altering cholinergic and dopaminergic interactions may be key in preventing METH relapse in humans.

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- Nicotine exposure during adolescence increased METH intake in adulthood
- Nicotine exposure during adolescence did not affect METH seeking behavior
- Low (0.16 mg/kg) but not high (0.64 mg/kg) nicotine exposure increased METH intake

Figure 1.

Mean total number of METH infusions ($\pm$ SEM) made by adult rats during self-administration training for METH on an FR 1 schedule of reinforcement. Rats were exposed to nicotine (0.16 or 0.64 mg/kg) or saline during adolescence (PD 35–50) and adulthood.

*Indicates a statistical difference from SAL-SAL group. † Indicates a statistical difference from 0.16–0.16 group.

Figure 2.

Mean total number of METH infusions ($\pm$ SEM) made by adult rats during self-administration training for METH on an FR 3 schedule of reinforcement. Rats were exposed to nicotine (0.16 or 0.64 mg/kg) or saline during adolescence (PD 35–50) and adulthood.

*Indicates statistical difference from SAL-SAL group; †Indicates different from 0.16–0.16 group.