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Short communication

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: SAL–SAL, 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). 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.

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 (Lenney 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

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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 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 an fixed ratio (FR) 1 schedule 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 gentamiacin and closed with nylon sutures. The metal end of the catheter was run 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 an 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, 1 s later, by a 4 s METH infusion. After each infusion, the active lever became inactive for 20 s, which was indicated by the absence of the house light. To progress from the FR1 to the FR3 schedule rats had to meet the criterion of receiving 10 infusions for at least two consecutive days.

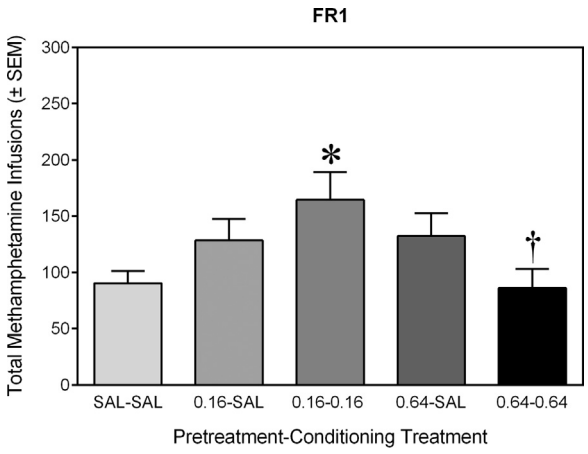

Fig. 1. Mean total number of METH infusions (±SEM) made by adult rats during self-administration training for METH on an FR 1 schedule of reinforcement. Rats were exposed to nicotine (0.16 or 0.64 mg/kg) or saline during adolescence (PD 35–50) and adulthood. * Indicates a significant difference from SAL–SAL group. † Indicates a significant difference from 0.16–0.16 group.

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 2 h 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 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 [$F(4,38) = 2.95$, $p < 0.05$, 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