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Research report

Reinstatement of methamphetamine conditioned place preference in nicotine-sensitized rats

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HIGHLIGHTS

- Reinstatement of methamphetamine-induced CPP varies as a function of dose.
- Prior exposure to nicotine did not alter methamphetamine-induced CPP.
- Nicotine given in combination with methamphetamine reinstated the preference.
- Nicotine may alter the rewarding effects of methamphetamine.

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ABSTRACT

The current experiments examined the effects of repeated nicotine prior to acquisition, extinction, and reinstatement of methamphetamine-induced conditioned place preference (CPP). Methamphetamine-induced (METH; 0.25, 0.5, or 1 mg/kg, s.c.) CPP was established using separate groups of adult male Sprague-Dawley rats with an unbiased conditioning procedure. Following extinction of METH CPP, drug-primed reinstatement (0, 0.25, 0.5 or 1 mg/kg, s.c.) of METH CPP was assessed in order to determine whether METH-induced reinstatement depends on the METH dose used to induce CPP. In a second experiment, separate groups of rats received nicotine (NIC; 0 or 0.2 mg/kg, s.c.) for 7 days prior to undergoing METH (0 or 0.5 mg/kg, s.c.) conditioning, extinction, and drug-primed reinstatement. Results indicate that METH-primed reinstatement varied as a function of dose such that priming with the conditioning dose did not reinstate CPP, but reinstatement was observed following priming doses of METH that were either lower or higher than the conditioning dose. Prior NIC exposure had no effect on METH CPP, extinction, or reinstatement. Interestingly, at a METH dose (0.5 mg/kg) that did not induce reinstatement alone, acute NIC (0.2 mg/kg) in combination with METH induced reinstatement, suggesting that NIC produced a leftward shift in the dose-response effect of METH to reinstate CPP. These studies indicate that prior NIC exposure may not be necessary for enhancement of the rewarding effects of METH, in contrast to previous self-administration reports.

1. Introduction

A vast majority of illicit drug users also smoke tobacco cigarettes. It has been reported that as many as 97% of methamphetamine (METH) users also use tobacco [1], with 88% also reporting regular past-week tobacco use [2]. Although no study to date has investigated the effects of METH on tobacco cigarette smoking, studies have shown that administration of either amphetamine or cocaine increases ad libitum cigarette smoking [3–5]. A recent review also found evidence for more severe health problems, increased stimulant dependence, and poorer treatment outcomes in psychostimulant users who also smoke tobacco cigarettes compared to those who do not [6].

Preclinical studies suggest possible interactions between METH and nicotine (NIC), a major addictive alkaloid in tobacco cigarettes. NIC substitutes fully for METH in rats trained to discriminate METH from saline (SAL), suggesting that METH and NIC share some discriminative stimulus properties [7,8]. In addition, repeated NIC exposure results in subsequent locomotor cross-sensitization in

Abbreviations: ANOVA, analysis of variance; CPP, conditioned place preference; GABA, gamma-aminobutyric acid; METH, methamphetamine; NIC, nicotine; SAL, saline (NaCl); VTA, ventral tegmental area.

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response to a METH challenge in mice [9]. Further, pretreatment with METH increases NIC self-administration in a biphasic manner [10] and nicotine reinstates METH-seeking behavior in rats previously exposed to NIC [11]. Thus, both clinical and preclinical studies suggest an interaction between NIC dependence and METH abuse. Further research on this possible interaction could lead to more efficacious treatments for METH abuse and dependence.

With the high rate of comorbidity between NIC and METH abuse, it is important to examine the effects of previous nicotine exposure on subsequent METH abuse. Several studies indicate that NIC increases both METH self-administration and METH-induced locomotor activity [9,11,12]. However, little is known about the role of conditioned cues on NIC-METH interactions. This is an important area of investigation for cue-elicited craving and relapse prevention, as exposure to NIC may reinstate not only NIC seeking, but also METH seeking. The purpose of the current experiments was to determine the effects of NIC on the drug-primed reinstatement of METH-induced conditioned place preference (METH CPP). The first experiment investigated reinstatement of METH CPP by priming injections of varying doses of METH (0.25–1.0 mg/kg). A second experiment investigated the effects of prior NIC administration on subsequent METH CPP and reinstatement. A low dose of NIC (0.2 mg/kg, s.c.) was used in this latter experiment because it reliably produces locomotor sensitization in our laboratory, as well as others [11,13,14]. Given the findings from previous self-administration results [11], it was hypothesized that NIC would reinstate METH CPP in NIC-exposed rats, but not in NIC-naïve rats.

2. Material and methods

2.1. Animals

Male Sprague-Dawley rats ($n = 72$) were acquired from Harlan Industries (Indianapolis, IN), weighing 250–275 g at the beginning of the experiment and were maintained in accordance with the University's Institutional Animal Care and Use Committee. Rats were double-housed in a temperature-controlled colony with a 12 h/12 h light/dark schedule (lights on at 0700). Animals had free access to food and water while in their home cages during the experiment. Rats were allowed to acclimate to housing for three days and were subsequently handled for approximately 3 min per day for a total of three days prior to experimental manipulations.

2.2. Drugs

(+)-METH HCl from the National Institute on Drug Abuse (Bethesda, MD) was prepared in SAL (0.9% NaCl). All METH doses are represented as salt weight. S(−)-NIC ditartrate (Sigma, St. Louis, MO) was prepared in SAL solution; a pH of 7.4 was obtained using NaOH. All NIC doses are represented as free-base weight. Both drugs were administered by subcutaneous injection in a volume of 1 ml/kg.

2.3. Apparatus

For assessment of CPP, a rectangular box (21 cm × 21 cm × 68 cm) divided into three chambers (ENV-013; MED Associates, St. Albans, VT) was used. The box had two large end chambers (21 cm × 28 cm) separated by removable guillotine doors from a middle chamber (21 cm × 12 cm). One end chamber had white walls and stainless steel mesh flooring. The other end chamber had black walls with stainless steel rod flooring. The middle chamber had gray walls, as well as a solid floor, and was a "neutral" chamber. Each end chamber contained six photobeams that were located 1.25 cm from the end wall and 5 cm apart. The middle gray chamber had three photobeams located 4.75 cm apart.

For assessment of locomotor activity, a square box (42 cm × 42 cm × 30 cm) consisting of clear acrylic walls and floor was used. Activity was recorded using an animal activity monitoring system with Versamax System software (AccuScan Instruments Inc., Columbus, OH). Inside the box, a horizontal 16 × 16 grid of photobeams with each beam 2.5 cm apart and 7.0 cm above the floor measured locomotor activity, expressed as distance (cm) traveled.

2.4. Experimental procedures

2.4.1. Experiment 1: reinstatement of extinguished METH CPP

The aim of this experiment was to determine if METH-induced reinstatement is dependent upon the METH dose used to induce CPP. Rats were given one session of habituation to the CPP chamber (day 1) during which they received SAL immediately before being placed into the neutral (gray) chamber and were allowed to explore all three chambers of the CPP apparatus for 15 min. The following day (day 2), the rats were given a pre-conditioning test to determine a baseline chamber preference. On this pre-conditioning test day, rats were administered SAL immediately before being placed into the neutral chamber and had access to all three chambers. The time spent in each chamber during this 15 min test was assessed and any animal which spent ≥80% of the total test time [after 15, 16] in either end chamber was considered to have an initial bias for one chamber and was excluded from further testing. On days 3–10, rats were randomly assigned to treatment groups and underwent conditioning sessions in a counterbalanced, unbiased fashion (i.e. regardless of initial preference, one half of the rats received METH in the black chamber and SAL in the white chamber; the other half received METH in the white chamber and SAL in the black chamber). During these conditioning sessions, the guillotine doors were closed and rats were confined to one of the end chambers. On alternating days, separate groups ($n = 13$–14 per group) received METH (0.25, 0.5, or 1.0 mg/kg, s.c.) injections paired with one of the end chambers and SAL administration paired with the opposite end chamber. Rats were placed into the appropriate chamber immediately following METH or SAL administration for a 30 min conditioning session for a total of eight sessions (i.e. four METH-paired and four SAL-paired). The end chamber that was paired with METH and the order of METH and SAL sessions was counterbalanced across rats. Following the last conditioning day, a post-conditioning test was used to assess each animal's preference. On this day (day 11), all rats were administered SAL immediately before being placed into the neutral chamber and were given free access to all three chambers. The time spent in each chamber during the 15 min test was assessed.

Days 12–19 were extinction sessions, during which SAL was paired with both chambers on alternating days for a total of eight, 30 min counterbalanced sessions (4 in the black chamber and 4 in the white chamber). Following the last extinction day, a post-extinction test was conducted to determine if each animal's preference for the METH-paired chamber was successfully extinguished, defined by <80% of the total test time in the METH-paired chamber (after the initial chamber preference criteria; i.e., time in METH-paired chamber divided by time in both METH- and SAL-paired chambers × 100). SAL was administered immediately before placing the animal into the neutral chamber and the time spent in each of the 3 chambers during the 15 min period was assessed. Any animal which spent ≥80% of the total test time in the METH-paired chamber was considered not extinguished and was excluded from reinstatement testing until the extinction criterion described above was met.

Days 20–35 were reinstatement test sessions. For each reinstatement test, rats were administered either SAL or METH (0.25, 0.5, or 1.0 mg/kg, s.c.) in a randomized order immediately before being placed into the neutral gray chamber. Each rat received each dose on separate reinstatement tests. During the test, animals were given free access to the entire apparatus and the time spent in each chamber was assessed. To ensure that the animals did not display a significant preference following the reinstatement session, each reinstatement test was separated by two extinction sessions during which rats were injected with SAL prior to placement in one of the end chambers on alternate days (i.e. each end chamber was paired with SAL once) and then underwent an additional baseline test following a SAL injection (no reinstatement). The experimental procedures for Experiment 1 are outlined in Table 1.

2.4.2. Experiment 2: reinstatement of METH-induced CPP in NIC-sensitized rats

The aim of this experiment was to determine if previous exposure to NIC would alter METH-seeking behavior. Throughout the first 7 days of this experiment, rats were administered either SAL (two groups of $n = 8$ each) or NIC (0.2 mg/kg, s.c; two groups of $n = 8$ each) immediately before being placed into a locomotor apparatus for 60 min sessions. Following the last day of locomotor activity monitoring, rats were given one day of habituation to the CPP apparatus followed by a pre-conditioning test as described in Experiment 1. Rats were then conditioned in a counterbalanced unbiased fashion in a similar manner to that described for Experiment 1 (days 10–17). The experimental design was a 2 × 2 (previous sensitization treatment × conditioning treatment) factorial that resulted in 4 experimental groups. Rats previously exposed to either NIC or SAL then underwent conditioning sessions with either METH (0.5 mg/kg, s.c.) or SAL (groups NIC-METH, NIC-SAL, SAL-METH, and SAL-SAL, respectively). For rats in the METH-conditioned groups ($n = 8$/group), METH (0.5 mg/kg, s.c.) administration was paired with one of the end chambers and SAL administration was paired with the opposite end chamber on alternating days for total of 8 sessions. For rats in the SAL-conditioned groups ($n = 8$/group), SAL administration was paired with one of the end chambers and SAL administration was also paired with the opposite end chamber on alternating days for a total of 8 sessions. All conditioning sessions were 30 min in length. This intermediate dose of METH was chosen based on the results from Experiment 1 showing that METH (0.5 mg/kg, s.c.) resulted in significant CPP, but administration of this dose did not produce reinstatement. SAL-conditioned animals were randomly assigned a pseudo "METH-paired chamber" and "SAL-paired chamber" in order to be consistent with METH-conditioning groups. Following the last conditioning day (day 18), a post-conditioning test was conducted during which rats received a SAL injection and were immediately placed into the neutral chamber as described in the first experiment.

Days 19–26 were extinction sessions identical to those described in Experiment 1. Following the last extinction day, rats were given a baseline (post-extinction) test on day 27 and were tested for METH-induced reinstatement on days 28–40