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Research report

Unique genetic factors influence sensitivity to the rewarding and aversive effects of methamphetamine versus cocaine

Noah R. Gubner[a], Cheryl Reed[a], Carrie S. McKinnon[a], Tamara J. Phillips[a,b,*]

[a] Department of Behavioral Neuroscience and Methamphetamine Abuse Research Center, Oregon Health & Science University, Portland, OR, USA
[b] Veterans Affairs Medical Center, Portland, OR, USA

HIGHLIGHTS

- Mice bred for high and low methamphetamine (MA) intake were used to study cocaine responses.
- These lines differ in sensitivity to MA conditioned reward and aversion.
- These lines did not differ in sensitivity to cocaine conditioned reward and aversion.
- A similar locomotor response previously found for MA was also found for cocaine.
- Unique genetic factors influence sensitivity to hedonic effects of MA and cocaine.

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ABSTRACT

Genetic factors significantly influence addiction-related phenotypes. This is supported by the successful bidirectional selective breeding of two replicate sets of mouse lines for amount of methamphetamine consumed. Some of the same genetic factors that influence methamphetamine consumption have been previously found also to influence sensitivity to the conditioned rewarding and aversive effects of methamphetamine. The goal of the current studies was to determine if some of the same genetic factors influence sensitivity to the conditioned rewarding and aversive effects of cocaine. Cocaine conditioned reward was examined in methamphetamine high drinking and low drinking line mice using a conditioned place preference procedure and cocaine conditioned aversion was measured using a conditioned taste aversion procedure. In addition, a general sensitivity measure, locomotor stimulant response to cocaine, was assessed in these lines; previous data indicated no difference between the selected lines in sensitivity to methamphetamine-induced stimulation. In contrast to robust differences for methamphetamine, the methamphetamine high and low drinking lines did not differ in sensitivity to either the rewarding or aversive effects of cocaine. They also exhibited comparable sensitivity to cocaine-induced locomotor stimulation. These data suggest that the genetic factors that influence sensitivity to the conditioned rewarding and aversive effects of methamphetamine in these lines of mice do not influence sensitivity to these effects of cocaine. Thus, different genetic factors may influence risk for methamphetamine versus cocaine use.

1. Introduction

Methamphetamine (MA) and cocaine (COC) have been classified as having similar pharmacological and behavioral profiles. However, COC and MA exhibit differences in mechanisms of action and pharmacokinetic profiles that could lead to differences in abuse potential. Thus, genetic factors that influence risk for their use may also differ.

COC can be generally characterized as a monoamine transporter blocker that prevents the reuptake of released monoamines, whereas MA can be generally characterized as a monoamine releaser. The end result of treatment with either drug is higher synaptic levels of these neurotransmitters [1]. COC has a shorter half-life than MA [2], which likely influences frequency of use. The subjective and cardiovascular effects also differ in onset and duration, with those after MA being more profound [3]. In addition, some users have reported a better "high" from MA than COC [4], which may have an impact on addiction potential. COC has been found to substitute for MA in drug discrimination paradigms [5],

* Corresponding author at: VA Medical Center, R&D 32, 3710 SW US Veterans Hospital Rd., Portland, OR 97239, USA. Tel.: +1 503 220 8262x56674; fax: +1 503 721 1029.
E-mail address: phillipt@ohsu.edu (T.J. Phillips).

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suggesting these two drugs have some similar subjective effects. However, habitual abusers tend to use COC or MA fairly exclusively [6,7], suggesting individual drug preferences. Although genetic influence on sensitivity and risk for abuse or dependence has been found for both MA [8,9] and COC [10,11], and mechanisms associated with their effects have been widely investigated, there is a lack of research addressing whether common genetic factors influence risk and responses to these two drugs. This has implications for prevention and treatment.

Our lab has created selected lines of mice for high and low MA drinking (MADR). Our data indicate that MA low drinking (MALDR) mice are insensitive to rewarding and reinforcing effects of MA, and are highly sensitive to aversive effects of MA, whereas the MA high drinking (MAHDR) mice show an opposite sensitivity profile [12–15]. Thus, some common genetic factors influence MA consumption and sensitivity to the rewarding and aversive effects of MA. The MADR lines provide a genetic model for testing the hypothesis that common genetic factors influence sensitivity to MA and COC. Selective breeding for MADR may have altered the frequency of genes relevant to unique effects of MA; for example, MA and COC differentially regulate vesicular monoamine transporter-2 (VMAT-2), involved in storage of dopamine in synaptic vesicles [1]. Alternatively, selection could have impacted common mechanisms, perhaps monoamine effects.

In the current studies, the MADR lines were tested for COC responses, using the same procedures previously used to examine MA conditioned responses [12–14]. Sensitivity to the aversive effects of COC was measured using a conditioned taste aversion procedure (CTA) and sensitivity to the rewarding effects of COC was measured using a conditioned place preference (CPP) procedure. In addition, sensitivity to the stimulant effect of COC was examined for comparison to previous data that showed no difference between the MADR lines in the acute stimulant response to MA [14]. We hypothesized that if a line difference was found, the MAHDR line would be more sensitive to the rewarding and less sensitive to the aversive effects of COC compared to the MALDR line, but they would not differ in sensitivity to the acute stimulant effects.

2. Materials and methods

2.1. Animals

Male and female mice from the second consecutive replicate of the short-term selectively bred MALDR and MAHDR lines were used. Short-term selected lines are bred using mass selection for only 4–5 generations [16]. This avoids excessive inbreeding at genetic loci not relevant to the selection phenotype (i.e., random drift). Consecutive replicates are created to test hypotheses derived from previous sets of the same type of selected line. We have demonstrated excellent replication of results for two sets of MADR lines bred two years apart [12–14]. The methods used to create the two sets of MADR lines are published [12,13]. Briefly, these lines were created from the F2 cross of the C57BL/6J (B6) and DBA/2J (D2) inbred mouse strains. Mice from the F2 were chosen for breeding (i.e., selected) based on amount of consumption of a 40 mg MA per liter of tap water solution, when it was offered along with a separate drinking tube containing plain tap water. The highest MA consuming F2 mice served as breeders for the MAHDR lines and the lowest MA consuming F2 mice served as the breeders for the MALDR lines. Selection was terminated after 5 generations and after this time, mice were randomly chosen for breeding to produce additional mice for testing. Mice used in the current studies were offspring of the replicate 2 lines of the fifth (S5) selection generation. Mice were weaned at 20–22 days of age and subsequently group housed with same sex littermates, 2–5 mice per cage, in standard mouse shoebox cages (28.5 cm × 17.5 cm × 12 cm) lined with Bed-o'Cobs® bedding (The Andersons, Inc., Maumee, OH, USA). Mice were given ad libitum access to water and food (LabDiet® 5001, PMI Nutrition International LLC, St. Louis, MO, USA) that was purchased from Animal Specialties Inc. (Hubbard, OR, USA). All mice were experiment- and drug-naïve prior to testing. All behavioral testing was conducted during the light phase of the 12:12 h light:dark cycle (lights on at 0600 h), between 0800 and 1600 h. Additional details regarding the mice that were used for each study are described with the results.

2.2. Drugs

Cocaine HCl (Sigma–Aldrich; St. Louis, MO, USA) was prepared on the day of testing in 0.9% saline (Baxter Healthcare Corporation, Deerfield, IL) and administered by i.p. injection.

2.3. Conditioned place preference (CPP)

Sensitivity to the rewarding effects of COC was measured using a standard unbiased CPP procedure, as previously described [12,13]. This CPP procedure was unbiased, since the assignment of the floor type paired with COC for each individual animal was not based on that individual's initial floor preference. The current study was designed to match the CPP methods used to assess MA CPP in the MADR lines. Previous studies have found no initial bias for these conditioning cues (grid or hole floor) in either the D2 or B6 strains [17], the progenitors of the MADR lines, or in large panels of inbred BXD strains derived from the B6 and D2 strains [18]. The 30 cm × 15 cm × 15 cm CPP chambers (San Diego Instruments, San Diego, CA, USA) consisted of clear plastic walls and exchangeable floor panels. Three different floor types were used in this study: a solid black plastic acrylic floor; a "grid" floor constructed of 2.3 mm stainless steel rods mounted 6.4 mm apart; and a "hole" floor constructed of a stainless steel panel with 6.4 mm round holes aligned with 9.5 mm staggered centers. A removable black plastic divider was used to confine animals to the right or left side of the chamber on conditioning sessions. Conditioning boxes were housed in illuminated and ventilated sound attenuating chambers during testing. During test sessions, activity and location of the mouse was measured by photocell interruptions recorded by a fully automated system.

The COC-induced CPP procedure matched that used for our published work for MA [12,13], with the exception that conditioning trial durations were 30 min, instead of 15 min, long. The longer trial duration was used because DBA/2J mice, one of the progenitor strains for the MADR lines, did not develop a COC-induced CPP using 15 min conditioning trials [19]. On day 1, to habituate the mice to handling and the CPP apparatus, all mice were given one, 5-min habituation session, during which the mouse was injected with saline and placed in the chamber with access to both sides (black plastic flooring on both sides). This solid black flooring was only used during the habituation session to allow the mice to acclimate to the CPP procedure and apparatus without exposing them to the floor types (grid and hole) used during subsequent conditioning sessions. For 12 alternating test sessions (excluding weekends), mice were conditioned with 10 mg/kg COC and saline, each paired with a distinct floor type (grid or hole); thus, there were 6 COC conditioning and 6 saline conditioning sessions. For each conditioning session, the mouse was injected with COC or saline and immediately placed on the appropriate floor type on one side of the apparatus for 30 min (floor type associated with COC, side of apparatus and whether COC or saline was given prior to the first conditioning session were counterbalanced). A 10 mg/kg dose of COC was chosen based on the