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Research report

Methamphetamine drinking microstructure in mice bred to drink high or low amounts of methamphetamine

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HIGHLIGHTS

- Genetic differences influence the microstructure of methamphetamine drinking.
- Breeding for high methamphetamine intake leads to greater and longer drinking bouts.
- Breeding for low methamphetamine intake leads to longer time between drinking bouts.
- Methamphetamine drinking patterns could predict genetic risk for higher intake.

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ABSTRACT

Genetic factors likely influence individual sensitivity to positive and negative effects of methamphetamine (MA) and risk for MA dependence. Genetic influence on MA consumption has been confirmed by selectively breeding mouse lines to consume high (MAHDR) or low (MALDR) amounts of MA, using a two-bottle choice MA drinking (MADR) procedure. Here, we employed a lickometer system to characterize the microstructure of MA (20, 40, and 80 mg/l) and water intake in MAHDR and MALDR mice in 4-h limited access sessions, during the initial 4 hours of the dark phase of their 12:12 h light:dark cycle. Licks at one-minute intervals and total volume consumed were recorded, and bout analysis was performed. MAHDR and MALDR mice consumed similar amounts of MA in mg/kg on the first day of access, but MAHDR mice consumed significantly more MA than MALDR mice during all subsequent sessions. The higher MA intake of MAHDR mice was associated with a larger number of MA bouts, longer bout duration, shorter interbout interval, and shorter latency to the first bout. In a separate 4-h limited access MA drinking study, MALDR and MAHDR mice had similar blood MA levels on the first day MA was offered, but MAHDR mice had higher blood MA levels on all subsequent days, which corresponded with MA intake. These data provide insight into the microstructure of MA intake in an animal model of differential genetic risk for MA consumption, which may be pertinent to MA use patterns relevant to genetic risk for MA dependence.

1. Introduction

Genetic factors may influence who is and is not at risk for developing a pattern of methamphetamine (MA) use leading to dependence. Several genetic variants in human populations have been identified and associated with MA abuse, dependence, and psychosis [1]. We have examined the heritability of MA drinking (MADR) in mouse lines that were selectively bred for oral consumption of either high (MAHDR) or low (MALDR) amounts of MA [2,3]. Selective breeding produced MAHDR lines that consume approximately 6 mg/kg of MA during an 18-h MA access period, compared to 0.5 mg/kg MA intake in MALDR mice [2,3]. Calculated heritability was 0.34 in the replicate 1 set of lines and 0.35 in replicate 2, indicating that ~35% of the variance in intake could be attributed to heritable genetic factors. In addition to higher consumption of the drug, MAHDR mice are more sensitive to the conditioned rewarding and reinforcing effects of MA, whereas MALDR mice are more sensitive to the aversive effects of MA [2,4]. The focus of the present study is on patterns of MA intake

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that may be informative with regard to genetic risk for further use.

Although we have examined the motivational drive for MA intake in our genetic model of high and low MA intake, we have not examined patterns of consumption during the time that MA drinking is established. Initial experiences are critical to further use and microstructural analysis of MA and water intake during this time period would provide information about the impact of differential genetic risk for intake on the acquisition of MA consumption. In previous work, MADR mice trained to perform an operant response to gain access to either a saccharin sweetened MA- or non-MA-containing tube did not differ in the amount of MA consumed during the first trial that it was offered. However, MALDR mice reduced their consumption during the next trial and the selected lines differed in MA consumption during all subsequent trials [5]. These data suggest that the MALDR line mice reduce their intake after experiencing pharmacological effects of MA that they perceive as aversive, rather than in response to taste or some other peripheral factor. Our previously published data, examining both taste factors and sensitivity to the aversive effects of MA, support this conclusion [2,3,5].

The microstructure of MA and water consumption was examined during 4-h limited access sessions using a lickometer system. The lickometer system provides precise time resolution of drinking behavior by continuously recording each lick of the sipper tube. By grouping these licks into bouts, several drinking measures can be obtained including number of drinking bouts, time between bouts, size of bout, and bout duration. Microstructural data using lickometer and similar systems have been commonly generated for ethanol and sucrose drinking [6–14]. In a separate study, we examined MA blood levels at time points that corresponded with the lickometer procedure. We hypothesized that similar to the operant oral self-administration data, the MADR lines would not differ in amount of MA consumed on the first day of MA access, but would diverge in amount consumed and in structural components (e.g., number and size of drinking bouts) of consumption from the MA-containing bottle, with subsequent access. We anticipated that blood MA levels would correspond with MA intake.

2. Materials and methods

2.1. Animals and husbandry

The MADR selected lines were created using mass and short-term selection. Mass selection was used to achieve a rapid response and selective breeding over few generations (i.e., short-term) was used to reduce the chance differential fixation of selection trait irrelevant genes within the lines [15]. Detailed selection procedures have previously been published [2,3]. Briefly, offspring from the F2 cross of C57BL6/J and DBA2/J inbred strains of mice were phenotyped in an 18-h two-bottle choice MA vs water drinking procedure for their MA consumption from a 20 mg/l then 40 mg/l solution, for 4 days per concentration. The highest and lowest MA consuming (in mg/kg MA from the 40 mg/l concentration) animals were used to establish breeders for the MAHDR and MALDR lines, respectively. Their first litter offspring were similarly tested and breeders were again selected. This procedure was followed in each subsequent generation for a total of 5 selection generations. Mice used in the current study were MA- and experiment-naïve offspring of fifth selection generation (S5) parents. The MADR lines were replicated sequentially so that data obtained in one set of lines could be extended in the subsequent set of lines. Results for some common traits have been obtained in both sets of lines and have been in good agreement [2,3]. The current study used replicate 2 MADR mice (MAHDR-2 and MALDR-2; the MADR-2 lines), as the replicate 1 lines had been retired when the current work was performed. A total of 44 adult female mice, age 61–114 days were used for the lickometer study and 42 adult female mice aged 99–124 days were used for the study measuring blood MA levels. Mice were housed with dam and sire until they were weaned at 21–23 days of age and were then grouped in cages with 2–5 same sex littermates. Female mice were used because they were more readily available than males at the time of this study. Importantly, previous studies have not identified significant sex differences for the difference in MA intake for either replicate set of the MADR lines [2,3]. Mice were housed in shoebox cages (28.5 cm × 17.5 cm × 12 cm) with Bed-O-Cob™ bedding (The Anderson Inc., Maumee, OH) and wire cage tops, and maintained at 21 ± 1 °C. They were placed on a reverse 12:12 h light:dark cycle (lights off at 08:30 h and on at 20:30 h) at least 2 weeks before the study began, and had free access to water and standard rodent diet (Purina 5001TM, Animal Specialties Inc., Hubbard, OR) at all times. The reverse light:dark cycle was used to allow drinking to be more conveniently assessed during the dark phase, when mice are more active and engage in more eating and drinking behavior. All procedures were performed in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals, and were approved by the Institutional Animal Care and Use Committee of the Portland Veterans Affairs Medical Center.

2.2. Drinking solutions

(+) Methamphetamine hydrochloride was purchased from Sigma (St. Louis, MO) and dissolved in tap water to 20, 40, and 80 mg/l concentrations. MA solutions were made fresh every 4 days.

2.3. Drinking pattern analysis

Fluid intake was measured in 24, custom-made acrylic plastic lickometer chambers (17.8 cm × 10.2 cm × 10.2 cm) that have been used in our previous studies [6,16]. The lickometer device was manufactured by MED Associates, Inc. (St Albans, VT). Each test chamber had a stainless steel wire grid floor (VWR; Tualatin, OR) and two small holes located in the back wall through which two metal sipper tubes were introduced. Tubes were secured to the chamber wall to reduce the potential for displacement by the mice and thus, reduce the recording of false intake volumes. A hinged acrylic plastic lid with ventilation holes covered each chamber. Stainless steel sippers (Anacore, Bellmore, NY) were attached to polystyrene serological pipettes (10 ml volume; VWR) to create drinking tubes. The pipettes were trimmed to a 6 ml capacity to allow them to fit properly behind the lickometer chambers. Tube volumes (0.1 ml accuracy) were recorded at the beginning and end of each 4-h drinking session.

The wire floor of the chamber and the metal sipper tubes form open electrical circuits connected to the lickometer device. A circuit is closed when an animal stands on the metal floor and makes contact by licking a sipper tube. A software program (MED-PC IV; MED Associates, Inc.) was used to automatically record cumulative sipper contacts. Individual animal cumulative lick records (total number of licks) were extracted using Soft CR version 4 (MED Associates, Inc.), and appetitive (latency to first bout) and consummatory (bout frequency, bout size, bout duration, inter-bout interval, bout lick rate) variables were extracted from the cumulative records using a custom data analysis program written for the online software R project for Statistical Computing (http://www.r-project.org). No previous data of this nature have been collected for MA, but based on multiple previous studies examining patterns of ethanol and sucrose drinking, a bout was defined as a series of at least 20 licks with less than 1 min separating each lick [6–9].