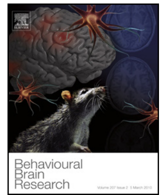
Behavioural Brain Research 256 (2013) 197–204

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr



Research report

Impaired memory and reduced sensitivity to the circadian period lengthening effects of methamphetamine in mice selected for high methamphetamine consumption

Reid H.J. Olsen[a], Charles N. Allen[a,b], Victor A. Derkach[c], Tamara J. Phillips[a,d,e], John K. Belknap[a,d,e], Jacob Raber[a,e,f,g,*]

[a] Department of Behavioral Neuroscience, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
[b] Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
[c] Vollum Institute, Oregon Health & Science University, 8131 SW Sam Jackson Park Road, Portland, OR 97239, USA
[d] Portland VA Medical Center, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
[e] Methamphetamine Abuse Research Center, Oregon Health & Science University, 8131 SW Sam Jackson Park Road, Portland, OR 97239, USA
[f] Department of Neurology, Oregon Health & Science University, 8131 SW Sam Jackson Park Road, Portland, OR 97239, USA
[g] Division of Neuroscience ONPRC, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA

HIGHLIGHTS

- MALDR mice show spatial memory retention.
- MAHDR mice do not show spatial memory retention.
- MAHDR mice have more GluR2 AMPA receptor subunits in the hippocampus.
- During 25 mg/L MA solution access, there is an increase in τ in MALDR mice.
- During 50 mg/L MA solution access, both lines show an increased τ.

GRAPHICAL ABSTRACT

ARTICLE INFO

Article history:
Received 20 June 2013
Received in revised form 2 August 2013
Accepted 6 August 2013
Available online 14 August 2013

Keywords:
Circadian
Water maze
Methamphetamine
Glutamate receptors
GluA1/2
Spatial memory

ABSTRACT

Drug abuse runs in families suggesting the involvement of genetic risk factors. Differences in addiction-related neurobiological systems, including learning and memory and circadian rhythms, may exist prior to developing addiction. We characterized the cognitive phenotypes and the free-running circadian period of mouse lines selectively bred for high methamphetamine (MA) drinking (MA high drinking or MAHDR) and low MA drinking (MA low drinking or MALDR). MA-naïve MALDR mice showed spatial memory retention while MAHDR mice did not. MA-naïve MAHDR mice had elevated hippocampal levels of the AMPA receptor subunits GluA2 (old terminology: GluR2), but not GluA1 (old terminology: GluR1). There were no line differences in the free running period (τ) when only water was available. During a 25 mg/L MA solution access period (vs water), there was an increase in τ in MALDR but not MAHDR mice, although MAHDR mice consumed significantly more MA. During a 50 mg/L MA solution access period (vs water), both lines showed an increased τ. There was a positive correlation between MA consumption and τ from baseline in MALDR, but not MAHDR, mice. Thus, a heritable proclivity for elevated MA self-administration may be associated with impairments in hippocampus-dependent memory and reduced sensitivity to effects of MA on lengthening of the circadian period.

© 2013 Elsevier B.V. All rights reserved.

* Corresponding author at: Department of Behavioral Neuroscience, Oregon Health & Science University, 8131 SW Sam Jackson Park Road, Portland, OR 97239, USA. Tel.: +1 503 494 1524; fax: +1 503 494 6877.
E-mail address: raberj@ohsu.edu (J. Raber).

0166-4328/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbr.2013.08.015

1. Introduction

Methamphetamine (MA) is a pyschostimulant, the abuse of which exerts a great physiological [1], social [2], and economic cost [3]. The increasing impacts of MA abuse are offset by prevention and treatment paradigms, which hinge on an understanding of MA addiction itself. In addicted individuals, consumption of a drug leads to changes in behavior that may result in an increase in drug consumption, and subsequently compulsive drug-seeking and drug-taking behavior, over time [4]. Multiple mechanisms are proposed to be involved. They include alterations in motivational states involving rewarding effects of the drug acting as a reinforcer of the behavior [5] and perturbations of learning and memory processes involved in drug-associated stimuli and hedonic and aversive effects of the drug [6]. In response to these perturbations, drug seeking and drug use might become compulsive by hijacking a component of the learning and memory system as part of an adaptive response [5].

Drug abuse runs in families, suggesting common environmental and/or genetic risk factors [7]. Differences in addiction-related neurobiological systems might exist prior to developing addiction. Mouse lines selectively bred for high MA drinking (MA high drinking or MAHDR) and low MA drinking (MA low drinking or MALDR) under two-bottle choice (MA vs water) conditions provide a unique resource for studying pre-existing genetic differences [8,9]. These lines have been validated as a model of genetically-determined differential MA reinforcement, reward and aversion. This validation is based on greater operant oral and intracranial self-administration of MA in MAHDR compared to MALDR mice, MA conditioned place preference that is present in MAHDR mice but completely absent in MALDR mice, and MA conditioned taste aversion that is present in MALDR mice but completely absent in MAHDR mice [8–11]. Other behavioral phenotypes that co-segregate with selection for MA consumption may offer additional insight into common neural systems that play a role in drug abuse and addiction.

Based on the putative involvement of learning and memory systems in drug addiction [12] and the impairments in learning and memory associated with MA use [13], we hypothesized that the MAHDR and MALDR lines would differ in cognitive performance. As measures of anxiety and exploratory behavior can potentially affect performance on cognitive tests, they were assessed as well. Substance abuse is associated with sleep disturbances [14] and exposure of the developing brain to MA increases the length of the circadian period in adulthood [15]. Therefore, we hypothesized that the free-running circadian period would be altered following access to a solution containing increasing MA concentrations as part of a two-bottle choice (vs water) condition. We further hypothesized that sensitivity to this disruption could be genetically related to voluntary MA consumption.

Finally, we hypothesized that in MA-naïve mice of the MA drinking lines, differences found in cognitive phenotype between the lines would be associated with line differences in hippocampal levels of proteins described below that are known to play an important role in hippocampus-dependent cognition. Expression of glutamate receptors 1 (GluA1; old terminology: GluR1) and 2 (GluA2; old terminology: GluR2) were quantified because of their involvement in circadian rhythmicity [16], the reward system [17], learning and memory [18], MA exposure [19], and addiction [20].

2. Methods

2.1. Animals

Two consecutive short-term selective breeding projects for MA drinking have been completed [8,9]. Short-term selection is an alternative approach to the creation of long-term selected lines, which are generally produced with the goal of maintaining the lines for many years (the long-sleep and short-sleep mouse lines bred for ethanol sensitivity and the alcohol preferring and non-preferring selected lines are examples). The goals for short-term lines are rapid production, and replacement by producing consecutive replicates to follow up interesting initial findings. This is a more feasible approach to limited resources and space for long-term maintenance. Selection for each set of lines was from a population of 120 mice (half of each sex) from the F2 cross of the C57BL/6J and DBA/2J inbred strains. These mice were offered 20 mg and subsequently 40 mg MA HCl/L in water ((+)-MA hydrochloride (Sigma, St. Louis, MO, USA) vs tap water, 18 h each day for 4 consecutive days per concentration. We found that access limited to 18 h each day increases MA intake, but does not result in significant weight loss (Phillips, unpublished data). Selection was based on average consumption (in mg/kg) of the 40 mg/L MA solution. Mass selection was used, which maximizes the response, and is the preferred method for short-term selections in which lines are terminated after 4–5 generations to avoid high rates of inbreeding that could result in the fixation of alleles not associated with the selection trait if selection was continued for additional generations. With mass selection, animals are chosen for breeding that have either the highest or lowest scores for the trait of interest, regardless of what families they belong to; however, mating of animals with common relatives is avoided to reduce inbreeding. Thus, the male and female mice with the highest MA intake were interbred to form the MAHDR (MA high drinking) line, and those mice with the lowest intake were bred to establish the MALDR (MA low drinking) line. Subsequent generations of mice were similarly tested and interbred. In both selections, maximal divergence was associated with intake of about 6 mg MA/kg/18 h in the MAHDR lines and close to 0 intake in the MALDR lines [8,9].

The mice used in the current study were MA-naïve second replicate line mice from the 5th selection generation showing maximal divergence [9]. They did not differ in age. Group sizes were MAHDR; male: $N = 9$ mice; female: $N = 13$ mice; and MALDR; male: $N = 8$ mice; female: $N = 8$ mice. Mice were maintained on a 12 h light/dark schedule (lights on at 06:00) and laboratory chow (PicoLab Rodent diet 20, # 5053; PMI Nutrition International, St. Louis MO, USA) and water were provided ad libitum. Behavioral testing took place during the light phase. All procedures complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the IACUC at Oregon Health & Science University. Mice were weaned and singly housed on postnatal day 20. As line differences in body weight might contribute to line differences in performance on cognitive tests, a subset of the animals were chosen at random and weighed every 3 days, over a period of 16 days (Male MAHDR, $N = 8$, Male MALDR, $N = 7$, Female MAHDR, $N = 11$, Female MALDR, $N = 4$) starting on postnatal day 30.50 ± 0.21, and ending on post-natal day 46.5 ± 0.21. Growth curve analysis ran concurrently over the span of behavioral testing.

2.2. Behavioral testing

The mice were behaviorally tested beginning shortly after weaning on postnatal day 31.6 ± 0.04 in the following order: exploratory behavior in the open field (16×16 in.), analyzed as beam breaks, for 10 min in the morning (day 1); measures of anxiety in the elevated zero maze for 10 min in the morning (day 2); novel object recognition (days 1–5); spatial learning and memory in the water maze (days 8–12); and contextual and cued fear conditioning (days 15 and 16). The object recognition test was performed as described [21]. All other tests were performed as described [22], with the following changes for the fear conditioning training paradigm. On the first day of fear conditioning, the mice were placed inside a dark fear-conditioning chamber. Chamber lights (at 100 lx) turned on at 0 s, followed by a 160 s habituation period and a subsequent 20-s (2800 Hz, 80 dB) tone (cue). A 2-s 0.35 mA footshock was administered at 178 s, co-terminating with the tone at 180 s. Chamber lights remained on for 15 s after CS–US pairing, terminating the trial at 195 s. Before each trial, materials used in the test were cleaned with 5% acetic acid, unless otherwise noted. After cognitive testing, mice were used for circadian testing. Due to limitations in terms of available mice and equipment to simultaneously test mice in a single circadian experiment, male mice were first used for circadian rhythm testing. As initial wheel-running data were not sufficient to calculate the free-running period of these mice, the experiment was aborted before administration of MA and the mice were killed by cervical dislocation for western blot analysis of hippocampal tissue (male MALDR, $N = 7$ mice, male MAHDR, $N = 6$ mice). Female mice were used for circadian rhythm testing (female MAHDR, $N = 8$ mice, female MALDR, $N = 6$ mice). The decision to subdivide animals by sex at this point was made for a number of reasons. Because line did not interact with sex during the current investigation or in the published literature for MA intake or other reward and aversion-related traits in these lines, we anticipated that such an effect in AMPAR and circadian period was unlikely. For all experiments, the researchers were blinded to the line of the animals.

2.3. Circadian rhythm testing

Following cognitive testing, a subgroup of female mice was individually housed in Nalgene cages equipped with running wheels and magnetic switches (Minimitter, Bend, OR, USA) to determine the circadian period. Only a subgroup was used, because of limitations on the number of mice the number of mice that can be simultaneously tested with our equipment. The cages were placed into Intellus Control System chambers (Percival Scientific, Perry, IA, USA) maintained at 21–22 °C on a

Download English Version:

https://daneshyari.com/en/article/6258775

Download Persian Version:

https://daneshyari.com/article/6258775

Daneshyari.com