Pharmacology, Biochemistry and Behavior 111 (2013) 51–57

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

96-hour methamphetamine self-administration in male and female rats: A novel model of human methamphetamine addiction ☆

Elyse M. Cornett *, Nicholas E. Goeders

Department of Pharmacology, Toxicology & Neuroscience, Louisiana State University Shreveport Health Sciences Center, Shreveport, LA 71103, United States

ARTICLE INFO

Article history:
Received 17 April 2013
Received in revised form 7 August 2013
Accepted 9 August 2013
Available online 17 August 2013

Keywords:
Methamphetamine
Self-administration
Binge
Addiction
Female
Escalation

ABSTRACT

Methamphetamine (MA) is a highly addictive psychostimulant drug of abuse for which no FDA-approved treatment exists. While high on MA, both male and female MA users report engaging in risky behaviors and are more likely to be involved in violent criminal activities and to engage in domestic and sexual violence. A unique aspect of MA is that it is typically used in binges. However, there is no animal model of MA self-administration that appears to represent a human MA self-administration binge. We recently developed a 96-hour MA self-administration paradigm in rats that more closely resembles how human MA users take the drug. Male and female rats were trained to self-administer MA for 96 consecutive hours for 5 weeks. Responding by female and male rats tended to escalate to binge-like behavior, as the animals responded continuously during their normal periods of activity as well as during their inactive periods for up to 72 h, followed by a crash of 6 or more hours. Thus, this 96-hour model of MA self-administration is a novel way to study MA addition in rats that may contribute to the development of improved treatments for recovering human MA users.

Published by Elsevier Inc.

1. Introduction

Methamphetamine (MA) is a highly addictive psychomotor stimulant. Methamphetamine is a unique drug of abuse for several reasons, not the least of which includes its user population. There has been a dramatic increase in MA use in the United States over the past 25 years, especially among women (Venios and Kelly, 2010). A recent survey by the Substance Abuse and Mental Health Services Administration (2011) showed that males are more likely to use marijuana, cocaine and hallucinogens, while men and women equally abuse MA. In addition, women tend to initiate MA use earlier than men and prefer to use MA over other drugs of abuse (Venios and Kelly, 2010). The use of MA has been linked to violence, risk-taking behaviors and criminal activity (Anderson and Bokor, 2012; Darke et al., 2008), even among female users. For example, women MA users are considered to be significantly more violent than men (Dluzen and Liu, 2008). While high on MA, both male and female MA users also report engaging in risky sexual behaviors (e.g., unprotected, with strangers, with multiple partners at once), decreased sexual inhibition, heightened sexual desire and arousal, and enhanced sexual pleasure, and they engage in prolonged sexual contact for hours and hours (Darke et al., 2008; Semple et al., 2002). These risky sexual behaviors contribute to the spread of HIV/AIDS (National Institute on Drug Abuse, 2012), which has been a major public health concern for several decades. These studies suggest that including female subjects in future research endeavors related to MA may be critical to identifying potential treatments for individuals with MA addiction. Unfortunately, there are still gaps within the drug addiction literature, especially related to female subjects, and thus, including female subjects in our investigation was paramount to this study.

Another unique characteristic of MA is the way in which the drug is used, which is typically in long, repeated binges followed by periods of sleep, often referred to as a crash. Although a clear definition of binge MA use is lacking in the current scientific literature (Cheng et al., 2010), self reports from MA users suggest that a binge can be described as taking MA for a long period of time "until you run out [of drug] or just can't physically do it anymore"(Semple et al., 2002). Accordingly, a "typical" MA binge may range from 3 to 22 days. Just as there is no clear definition of a MA binge in the literature, there also are no published models of MA self-administration in animals that are proposed to represent a MA binge and crash.

There have been several published reports of rats being exposed to long access MA for 6 h or more (Jang et al., 2013; Krasnova et al., 2010; Kuczenski et al., 2009; Schwendt et al., 2009), but none have reported a binge and crash behavior that is seen in human MA users. A key component of this binge and crash behavior may be the availability of drug to the animal in current model paradigms. Several reports have established that short access to drug (1 or 2 h) produces a pattern of intake that is stable and low (Ahmed and Koob, 1998; Kitamura et al., 2006; Schwendt et al., 2009), whereas rats exposed to extended access (6 h or more) show an escalation of intake and even binge-like patterns

☆ Conflict of interest: The authors declare no competing financial interests.

* Corresponding author at: 1501 Kings Highway, Department of Pharmacology, Toxicology & Neuroscience, Louisiana State University Shreveport Health Sciences Center, Shreveport, Louisiana 71103, United States. Tel.: +1 248 515 9211.
E-mail addresses: ecorne@lsuhsc.edu (E.M. Cornett), ngoede@lsuhsc.edu (N.E. Goeders).

0091-3057/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.pbb.2013.08.005

(Ahmed and Koob, 1998; Bozarth and Wise, 1985; Johanson et al., 1976; Kitamura et al., 2006; Mantsch et al., 2004). This is also consistent with reports that unrestricted access to MA and other drugs of abuse can lead to increases in drug taking in humans (Culbertson et al., 2010; Gawin and Ellinwood, 1989; Kramer et al., 1967). As we demonstrate below, escalation occurs in rats showing binge and crash-like behaviors, suggesting that escalation is a necessary component of addictive behavior. Since human MA users exhibit escalation, binge and crash behaviors, a model that reflects all of these key behavioral components would be useful to drug addiction research. Therefore, the objective of these experiments was to create and validate a novel animal model of MA self-administration that generates binge-like behavior followed by a crash.

The development of such a model is also important in the search for successful treatments for recovering MA users since most drugs that were reported as being successful in reducing MA self-administration in animals failed to translate to human MA addiction. This may be due to the fact that these studies used self-administration paradigms that did not reflect human MA use patterns. For example, gamma-vinyl-GABA (GVG), an irreversible GABA-transaminase inhibitor, has been shown to decrease MA-induced conditioned place preference (DeMarco et al., 2009), which when tested on MA-dependent volunteers, did not reduce MA craving (De La Garza et al., 2009). Similarly, Aripiprazole, an antipsychotic with partial dopamine receptor 2 agonism, decreased extracellular dopamine levels in MA-sensitized, fear-conditioned rats (Oshibuchi et al., 2009). However, Aripiprazole increased some stimulatory and rewarding effects induced by acute administration of MA in MA-dependent volunteers (Newton et al., 2008), suggesting that this treatment may not be useful for individuals recovering from MA addiction. Perhaps if experiments investigating potential pharmacological treatments for MA addiction utilized paradigms that reflected the human pattern of MA use, the process of identifying treatments for testing in human subjects with MA addiction would be more informative. Our 96-hour MA self-administration paradigm addresses the need for a novel model that has predictive validity, and therefore, may increase the efficacy of translational research from animals to human MA users. The goal of the experiments presented below was to explore the effects of 96-hour MA self-administration sessions on the drug-taking behavior of male and female rats and to determine if this model replicated the "binge and crash" behavior that is reported by human MA users.

2. Materials and methods

2.1. Subjects

Adult male (n = 10) and female (n = 7) Wistar rats (Harlan Sprague Dawley, Indianapolis, IN), aged 80–100 days, were free fed until they reached a minimum weight of 390 g for males and 290 g for females. The rats were subsequently maintained at 85 to 90% of their free-feeding body weights (330 g for males and 245 g for females) with free access to water as previously described (Goeders et al., 2012; Goeders and Guerin, 2008). Each rat was implanted with a chronic indwelling jugular catheter (Goeders and Clampitt, 2002) and allowed a minimum of five days to recover following surgery. Rats were singly housed in cages equipped with a laminar flow unit and air filter in a temperature- and humidity-controlled, AALAC-accredited animal care facility on a reversed 12-hour light, 12-hour dark cycle (lights on at 18:00). All procedures were carried out in accordance with the "Public Health Services Policy on Humane Care and Use of Laboratory Animals" and the "Guide for the Care and Use of Laboratory Animals" Eighth Edition, 2011 and were approved by the LSUHSC-S Institutional Animal Care and Use Committee.

2.2. Equipment

Behavioral experiments were conducted in standard Plexiglas and stainless steel, sound-attenuating operant conditioning chambers (Med-Associates, St. Albans, VT). Each experimental chamber was equipped with two response levers mounted on one wall of the chamber, and a stimulus light was located above each lever. The chamber was also equipped with an exhaust fan to provide ventilation and to decrease extraneous sounds to the animal. An overhead light was used to simulate a 12-hour light/dark period within the operant chamber. The chambers also contained water bottles, and the rats received fresh tap water each Monday. The water level was also visually monitored each day, and replenished when necessary. The rats were fed once per day in the operant chambers, just as they were fed in their home cages (14 g of food, standard rodent chow, Harlan Teklad, Madison, WI, USA). An IBM-compatible computer and interface were used to run the programs and collect the data.

2.3. Self-administration training

The rats were connected to the self-administration milieu via the indwelling jugular catheter. Tygon tubing, with a protective spring leash covering, was attached to the catheter. The tygon tubing was connected to a dual channel fluid swivel (Instech, Plymouth Meeting, PA) at the top of the chamber and continued outside the chamber where it was attached to a 60 mL drug-delivery syringe contained in a motor-driven pump. These syringes were closely monitored and replaced with new syringes containing MA before they became empty (i.e., when there was no less than 5 mL left in the syringe). Rats were trained to self-administer MA by pressing one of the response levers (i.e., the "active" lever) under a fixed-ratio 1 (FR1) schedule of reinforcement Monday through Friday, 24 h a day for 4 days (i.e., 96 h). The self-administration session started on Mondays at ~11:00 AM and ended on Fridays at ~11:00 AM. At the start of each session, a stimulus light above the active lever was illuminated to indicate the availability of MA. One depression of the active lever resulted in an intravenous infusion of MA (0.06 mg/kg/infusion) delivered in 200 μL 0.9% heparinized NaCl over 0.83 s. Two separate concentrated stock solutions of MA were prepared, one for males with an average weight of 330 g and one for females with an average weight of 245 g. Since the rats were food-restricted, we could maintain stable body weights at approximately 330 g for males and 245 g for females (i.e., approximately 85% of their free-feeding body weights). Thus, the male and female rats received MA from separate stock solutions that delivered the same concentration of MA based on body weight (i.e., 0.06 mg/kg/inf). A 20-second timeout period followed each infusion. The stimulus light above the active lever was darkened during the infusion and timeout period and was illuminated again once the timeout ended. Responses on the inactive lever resulted in no programmed consequences at any time. Upon completion of the 96-hour session on Friday mornings, the rats were placed into their home cages for 72 h where they had no access to MA. The following Monday at ~11:00 AM, the rats were placed back into the self-administration chamber and another 96-hour session was started. The rats completed 5 consecutive weeks under this protocol.

2.4. Drugs

Methamphetamine was obtained from the National Institute of Drug Abuse (Research Triangle Park, NC, USA).

2.5. Data analysis

All data were plotted and analyzed using GraphPad Prism, except for the cumulative records, which were plotted using SigmaPlot. All data, except cumulative records, were analyzed using a *t*-test, one-way ANOVA or two-way ANOVA using Tukey's post hoc test, as appropriate. For analysis purposes, a crash is defined as lack of lever presses for 6 h or longer, and a binge is any lever pressing that occurred for 24 h or more before the crash.