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The pharmacokinetics of methamphetamine self-administration in male and female rats

Alessandra Milesi-Hallé [1], Michael D. Hambuchen, Donald E. McMillan [2], S. Michael Owens *

Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, 4301 W. Markham, Little Rock, AR 72205, USA

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ABSTRACT

Background: Because methamphetamine (METH) pharmacokinetics after single iv doses show significant differences between male and female rats, we hypothesized that pharmacokinetic differences in METH disposition could be a contributing factor to the patterns of METH self-administration behaviors in rats.
Methods: For the studies, we used a passive (non-contingent) METH dosing schedule consisting of 27 METH iv bolus injections (0.048 mg/kg) over 2 h derived from a previous active (contingent) METH self-administration behavioral study in male rats. After METH dosing of male and female Sprague-Dawley rats ($n = 5$/group), METH and amphetamine serum concentrations were determined by LC–MS/MS. Pharmacokinetic analysis, including predictive mathematical simulations of the data, was then conducted.
Results: Male and female rats achieved relatively stable METH serum concentrations within 20 min, which remained constant from 20 to 120 min. While not statistically different, METH clearance and volume of distribution values for females were 25% and 33% lower (respectively) than males. Linear regression analysis of predicted METH concentrations from pharmacokinetic simulations versus observed concentrations showed a substantially better correlation with male data than female data ($r^2 = 0.71$ vs. 0.56; slope = 0.95 vs. 0.45, respectively). At 120 min, the time of predicted peak METH serum concentrations, female values were 42% higher than expected, while male values were within 3%.
Conclusions: Unlike METH male pharmacokinetic data, the female data was less predictable during multiple METH administrations and produced overall higher than expected METH concentrations. These findings demonstrate that METH pharmacokinetics could contribute to differences in METH self-administration behaviors in rats.

1. Introduction

Studies of (+)-methamphetamine (METH) human abuse patterns have helped delineate the characteristics of METH use (Cho and Melega, 2002; Comer et al., 2001; Hart et al., 2001; Melega et al., 2007; Mendelson et al., 1995). These data suggest METH abuse typically begins with low doses, taken over relatively long intervals of time (Cho and Melega, 2002). Too frequently, this introductory phase is followed by patterns of "binge" use with a quick progression to larger doses and shorter time intervals between doses.

Sex differences are found in a variety of drug abuse models, including psychostimulant self-administration paradigms. For instance, during training female rats acquire heroin and cocaine self-administration behavior in fewer days than males (Lynch and Carroll, 1999) and females display greater locomotor activity following cocaine (Quiñones-Jenab et al., 1999), amphetamine (AMP; Becker, 1999), or METH administration (Milesi-Hallé et al., 2005, 2007; Schindler et al., 2002). In METH self-administration studies, Long–Evans female rats are more vulnerable to acquisition of self-administration behavior and appear more motivated to maintain self-administration than male rats (Roth and Carroll, 2004). Other investigators find that compared to male Wistar rats, females are equally susceptible to METH-induced memory deficits and exhibit higher METH intake and greater relapse to METH-seeking (Reichel

* Corresponding author at: Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, 4301 W. Markham #611, Little Rock, AR 72205, USA. Tel.: +1 501 686 5487; fax: +1 501 526 4618.
E-mail addresses: milesihalle@comcast.net (A. Milesi-Hallé), hambuchenmichaeld@uams.edu (M.D. Hambuchen), demamcmillan@comcast.net (D.E. McMillan), mowens@uams.edu (S. Michael Owens).
[1] Current address: Miami Children's Hospital, Department of Child Neurology, 3200 SW 60th Ct., Suite 302, Miami, FL 33155, USA.
[2] 11 Twin Oaks Lane, Isle of Palms, SC 29451, USA.

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et al., 2012). This mirrors aspects of human self-administration studies in which low dose (8–10 mg) AMP administration is a reinforcer in women, but not men (Vansickel et al., 2010).

While neuroendocrine mechanisms could play a role in the different propensities for male and female rats to self-administer METH, pharmacokinetic mechanisms could also be a factor. Sex differences in METH disposition in male and female Sprague-Dawley rats (Milesi-Hallé et al., 2005, 2007) include a faster METH total clearance (CL_T) and a greater metabolic conversion of METH to AMP (a pharmacologically active metabolite) in male rats. The female Sprague-Dawley rats also have a lower metabolic clearance of METH, and a greater urinary excretion of unchanged METH (Milesi-Hallé et al., 2005).

The current studies were designed to both determine if the pharmacokinetics of METH could play a significant role in the sexual dimorphism of METH self-administration and if simulations of multiple dosing studies could be used to predict serum METH concentrations. To understand the interaction between the sex differences in METH pharmacokinetics and self-administration in rats, a pharmacokinetic model of passive (non-contingent; Jacobs et al., 2003) METH self-administration was derived from actual patterns of active (contingent) METH self-administration in male Sprague-Dawley rats (McMillan et al., 2004). Using this dosing protocol, the pharmacokinetic profiles of METH and AMP were then characterized in both male and female rats. Simulations of METH concentration versus time profiles using pharmacokinetic modeling software were also performed to evaluate the applicability of pharmacokinetic simulations to accurately predict METH concentrations achieved during a METH multiple-dosing protocol.

2. Materials and methods

2.1. Drugs and chemicals

(+)-Methamphetamine hydrochloride was obtained from the National Institute on Drug Abuse (Rockville, MD). (±)-Amphetamine-d_{11} and other chemicals were purchased from Sigma Chemical Company (St. Louis, MO). All other reagents were purchased from Thermo Fisher Scientific Inc. (Waltham, MA), unless otherwise noted. All drug concentrations are expressed as the free base form. METH doses for iv injections were prepared in 0.9% NaCl.

2.2. Development of METH self-administration dosing regimen in rats

The METH unit dose, time of dosing, and choice of patterns of METH administration used in the current studies were derived from previous experiments in our laboratory with male Sprague-Dawley rats (McMillan et al., 2004). To aid understanding of the current experimental METH dosing protocol, the key features are as follows. Male Sprague-Dawley rats ($n = 3$) were trained to press levers that delivered food pellets. After responding was established, the schedule was changed to deliver a food pellet after every third response (fixed-ratio [FR3] schedule). After one session under this FR3 schedule, an iv catheter was implanted into each rat's femoral vein under anesthesia.

Subsequently, METH was made available for self-administration under the FR3 schedule via a syringe pump, mounted over the test chamber and connected to the rat's catheter through polyethylene tubing. During training sessions, male rats could self-administer METH unit doses of 0.048 mg/kg under the FR3 schedule. The injection volume was approximately 0.07 ml, injected over 1.3 s; slight volume adjustments were made to correct for body weight differences. Rats were considered to have achieved stable behavior when no significant changes in the rates of responding were observed over four consecutive self-administration sessions. Individual patterns of activity are shown in Fig. 1A.

2.3. Animals

Male and freely cycling female Sprague-Dawley rats used in these studies were purchased from Hilltop Laboratory Animals Inc. (Scottsdale, PA). Rats were surgically implanted with femoral vein and external jugular vein catheters (Silastic medical-grade tubing, 0.020-in inner diameter and 0.037-in outer diameter; Dow Corning, Midland, MI). Catheters were kept below the skin surface for transport from the vendor and exposed under halothane anesthesia one day before the first experimental procedure. Catheters were kept patent by a daily saline flush (0.2 ml) followed by saline containing 25 U of heparin. Male and female rats were housed in separate cubicles. Each rat was housed in individual cages with a 12-h light/dark cycle, 22 °C environment with free access to water and fed approximately 20 g of pellets daily. This maintained female body weights between 250 and 280 g and male body weights between 270 and 300 g. All studies were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals*, as adopted and promulgated by the National Institutes of Health. All experiments were performed with the approval of the Animal Care and Use Committee of the University of Arkansas for Medical Sciences.

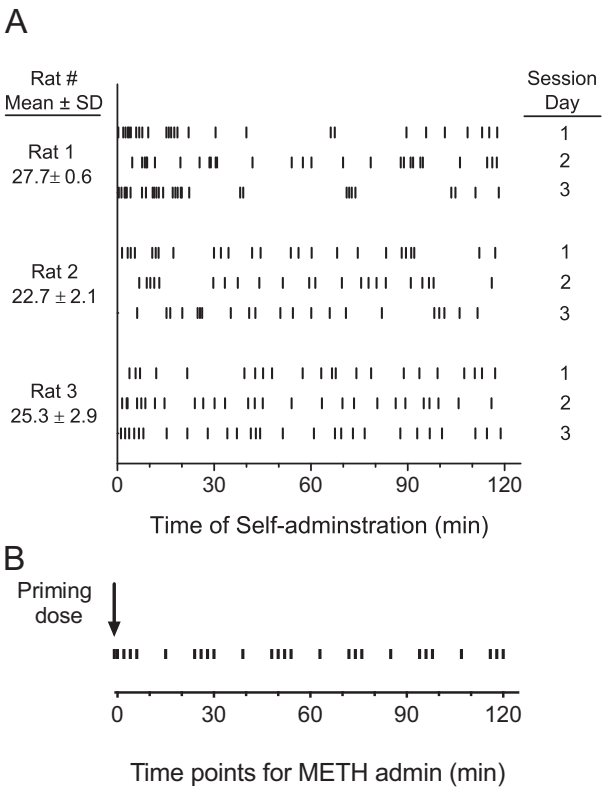

Fig. 1. (A) Injections self-administered by rats in 2-h sessions over three days (McMillan et al., 2004). (B) Drug administration protocol for the current study based on data from male rats that self-administered METH in 2-h behavioral sessions (see (A)).

2.4. Behavioral habituation and experimental apparatus for the pharmacokinetic studies

One week prior to experiments, rats were acclimated to metabolism cages (Nalgene Supply, Rochester, NY) and to harnesses (Instech Laboratories, Plymouth Meeting, PA) for 6 h/day. The rat's femoral vein catheter was used for drug administration and the jugular vein catheter was used for blood collection. On the first day of the experiment, the infusion harnesses were connected to a tether that protected two tubing extensions. The drug administration extension (0.023-in inner diameter and 0.038-in outer diameter; Intramedic® Polyethylene Tubing, Becton Dickinson, Parsippany, NJ) was attached to the rat's femoral vein catheter. The blood withdrawal extension was attached to the rat's jugular vein catheter. The rat was then placed in the metabolic cage and the tether was attached to a swivel. This allowed free movement in the cage during drug administration and blood sampling. The METH solution (0.2 mg/ml) was dispensed from a 500 μl dead volume syringe (Hamilton Company, Reno, NV) via a polyethylene extension attached to a programmable Harvard infusion pump (Harvard Apparatus, Holliston, MA).

2.5. Drug administration and blood sampling protocol

Rats in the prototype self-administration studies (McMillan et al., 2004) were shown to promptly achieve METH self-administration behavior. Because the protocol used by McMillan et al. included a METH priming dose before each session, rats in the current studies received one dose of 0.048 mg/kg METH 1 min before the beginning of the self-administration modeling session (Fig. 1). On average, these rats self-administered 26 injections of 0.048 mg/kg METH during the 2-h sessions (Fig. 1A). Including the priming dose, the total number of injections was 27. The average values for their inter-injection intervals and frequency of drug self-administration were also derived from the METH multiple injection protocol. Fig. 1B shows the estimated average METH self-administration patterns derived from Fig. 1A. METH doses were injected via femoral vein at −1, 0, 2, 4, 6, 15, 24, 26, 28, 30, 39, 48, 50, 52, 54, 63, 72, 74, 76, 85, 94, 96, 98, 107, 116, 118 and 120 min. The