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The neurochemical consequences of methamphetamine self-administration in male and female rats

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Abstract

Background—Methamphetamine (METH) is an addictive substance that is used in both males and females. Few preclinical studies have focused on understanding sex-differences in the neurochemical consequences of contingent METH. The purpose of the current study was to investigate potential sex-differences in the neurochemical consequences of METH self-administration.

Methods—Male and female adult rats were given extended access to METH or saline self-administration for 7 d. Following self-administration, hippocampal brain-derived neurotrophic factor (BDNF) and striatal dopamine transporter (DAT) were assessed via western blotting.

Results—Male and female rats had similar METH intake. METH self-administration reduced striatal DAT in both sexes, but only males that self-administered METH had elevated hippocampal BDNF levels.

Conclusions—Sex-differences exist in the neurochemical consequences of METH self-administration. These differences may lead to sex-specific vulnerability to the toxic effects of METH.

Keywords

Methamphetamine; female; self-administration; dopamine transporter; brain-derived neurotrophic factor

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Author Disclosures

Contributors

Participated in research design: McFadden and Johansen; Performed data analysis: McFadden and Johansen; Wrote or contributed to the writing of the manuscript: McFadden and Johansen; Conducted experiments: McFadden and Johansen; All authors contributed to and have approved the final manuscript.

Conflict of Interest

No conflict declared.

1.0 Introduction

The use of the highly addictive psychostimulant, methamphetamine (METH), occurs in both genders. Within the United States, females make up approximately 40% of lifetime METH users and approximately 50% of adolescent METH users (Chen et al., 2014). Recent studies suggest that gender differences exist in the use of METH, and its behavioral and psychological effects. Reports suggest that females start using METH at a younger age, transition from recreational use to addiction more quickly, and initiate the injection METH earlier than their male counterparts (Dluzen and Liu, 2008; Hadland et al., 2010; Liu et al., 2013; Rawson et al., 2005). Drug craving was also significantly correlated with depression and anxiety measures in male METH users but not females (Hartwell et al., 2016). Increased rates of depression, psychosis, and suicide have also been reported in females compared to males (Glasner-Edwards et al., 2008AB; Mahoney et al., 2010). Female METH users also reported a greater severity of drug use and psychological burden than their male counterpart (Simpson et al., 2016), further demonstrating the importance of investigating gender differences in METH users.

Recent clinical findings suggest that female METH/stimulant users show greater changes in the brain compared to their male counterparts. Female METH users currently in abstinence had reductions in hippocampal volumes compared to control females, whereas no difference was observed between METH-abusing and control male subjects (Du et al., 2015). Furthermore, female METH users had significantly lower phosphocreatine levels in the frontal lobe compared to male METH users (Sung et al., 2013). Researchers have also found that female METH/stimulant users displayed wide-spread reductions in grey matter volumes following prolonged abstinence (Regner et al., 2015). These changes in the female brain may in turn contribute to addictive behaviors and an increased risk of neurodegenerative diseases later in life.

Similar to findings in humans, preclinical studies utilizing METH self-administration have found sex-differences in drug use parameters. Female rats acquired METH self-administration more quickly than males (Kucerova et al., 2009; Reichel et al., 2012; Roth and Carroll, 2004). Further, female rats with a history of METH self-administration more vigorously reinstated drug-seeking compared to males (Cox et al., 2013; Holtz et al., 2012; Reichel et al., 2012). However, few studies have investigated the neurochemical consequences of METH self-administration in male and female rats. Previous research in male rats suggests METH self-administration increases brain-derived neurotrophic factor (BDNF) in various areas of the brain which may reduce the toxic effects of METH including attenuating the reduction of dopamine transporter (DAT) in the striatum (Krasnova et al., 2013; McFadden et al., 2014). This increase in BDNF declines during abstinences from METH (Krasnova et al., 2013). Therefore, the current study investigated the acute neurochemical consequences of METH self-administration in male and female rats.

2.0 Methods

2.1 Animals

Male and female Sprague-Dawley rats (postnatal day 59–62; Charles River Laboratories) were housed two rats/cage. After surgery, rats were individually housed in transparent plastic cages. Water was available *ad libitum*. During food training, rats were food restricted such that no rat dropped below 90% of their starting body weight. Rats were maintained in a 14:10 hour light/dark cycle. Animals were euthanized by rapid decapitation. All experiments were approved by the University of Utah's Institutional Animal Care and Use Committee, in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2 Drugs

Racemic-METH hydrochloride (supplied by the National Institute on Drug Abuse, Research Triangle Institute, Research Triangle Park, NC) was dissolved in 0.9% sterile saline and is expressed as free base. Rats were anesthetized using ketamine (90 mg/kg; Hospira Inc., Lake Forest, IL, USA) and xylazine (5–7 mg/kg; Sigma-Aldrich, St. Louis, MO, USA). Heparinized saline (63.33 U/ml; Sigma, St. Louis, MO, USA) was used to dissolve the antibiotic cefazolin (10 mg/ml; Schein Pharmaceutical, Florham Park, NJ, USA). Flunixin meglumine (1.1 mg/kg; MWI Veterinary Supply, Meridian, ID, USA) was given for post-surgery analgesia. Methohexital sodium (10 mg/mL; JHP Pharmaceuticals, Rochester, MI) was used to assess catheter patency.

2.3 Food Training and Surgery

Food training and self-administration occurred in an operant chamber as previously described (McFadden et al., 2012 AB). Prior to surgery, each rat was trained to press a lever for a 45-mg food pellet during four overnight 14-h sessions. Following food training, an indwelling catheter (see Frankel et al., 2008 for construction details) was implanted. Flunixin meglumine was given on the day of the surgery and the day following the surgery. Immediately following surgery and daily thereafter, each rat was infused with 0.1 ml of cefazolin, 0.05 ml of heparinized saline, and 0.05 ml of heparinized glycerol. Catheter patency was confirmed by infusing 0.1 ml (10 mg/ml) of methohexital sodium on the day prior to self-administration in all animals and throughout at signs of a potential loss in patency.

2.4 Self-Administration

Rats underwent 7 days of self-administration (8 h/session; FR1; 0.12 mg/infusion METH for males, 0.09 mg/infusion METH for females, or 10 μ l saline) during the light cycle in a room maintained at $28\pm1^{\circ}\text{C}$ to promote lever pressing (Cornish et al., 2008). An active lever press resulted in the retraction of the levers, a 10 μ l infusion of saline or METH over 5 s, followed by an additional 20 s of retracted levers as described previously (McFadden et al., 2012A). Rectal temperatures were recorded approximately 30 minutes following each session (Physitemp Instruments, Clifton, NJ). Animals were sacrificed 1 hour after the end of the

last self-administration session, brains were removed and hemisected, and the dorsal striatum and hippocampus was dissected from the left hemisphere.

2.5 Western Blotting

Synaptosomes were prepared as previously described (Hadlock et al., 2009; McFadden et al., 2014). Equal quantities of protein (10 µg) were loaded into each well of a 4 to 12% NuPAGE Novex Bis-Tris Midi gradient gel (Invitrogen, Carlsbad, CA) and electrophoresed using a XCell4 Surelock Midi-cell (Invitrogen). Membranes were blocked for 45 minutes with Starting Block Blocking Buffer (Pierce Chemical, Rockford, IL) and incubated for 1 hour at room temperature with an anti-brain-derived neurotrophic factor (BDNF) polyclonal (1:1000; Santa Cruz Biotechnology, Santa Cruz, CA, USA) or anti-dopamine transporter (DAT) polyclonal antibody (C-20; 1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Membranes were then washed and developed as previously described (McFadden et al., 2014). The resulting band densities were normalized to the percentage of average saline female immunoreactivity for ease of comparisons. The Bradford Protein Assay was used to quantify protein concentrations.

2.6 Statistical Analysis

Statistical analysis was conducted in SAS Studios. Only METH rats that met the criteria for high pressers (1: average of more than 10 active lever presses per day; and 2: the ratio of active/inactive lever presses of 2:1) were included in analysis, resulting in the exclusion of one male. Drug intake was normalized to the individual animal's body weight (kg) on the day of the session. Statistical analyses among groups were conducted using an analysis of variance (ANOVA) or repeated-measures ANOVA followed by a Newman-Keuls posthoc analyses. The data represent means $\pm$ standard error of the mean (S.E.M.) of 10–11 rats/group.

3.0 Results

Saline self-administering rats decreased active lever pressing over the course of the 7 d, whereas METH rats increased lever pressing (Group $\times$ Day: $F(6,228)=26.44$, $p<0.05$; Figure 1A). No sex differences were found (Sex: $F(1,28)=1.74$, ns; Sex $\times$ Day: $F(6,228)=0.49$, ns; Sex $\times$ Group $\times$ Day: $F(6,228)=0.46$, ns). Due to sex-differences in body weight, daily METH intake was normalized to body weight. Male and female rats increased daily METH intake over the course of the 7 days ($F(6,108)=6.35$, $p<0.05$; Figure 1B), but the increase was similar between the sexes (Sex: $F(1,108)=0.14$, ns; Sex $\times$ Day: $F(6, 108)=0.70$, ns). However, female rats and METH rats had higher body temperatures on Days 2–7 and Days 3–7 of self-administration, respectively (Sex $\times$ Day: $F(6,228)=3.04$, $p<0.05$; Group $\times$ Day: $F(6,228)=9.78$, $p<0.05$; Figure 1C). Given the unique temperature profiles between groups, body temperatures were analyzed separately. Further analysis found among METH self-administering rats, female rats had increasing daily body temperatures whereas male rats had stable body temperatures (METH-Sex: $F(1,18)=18.84$, $p<0.05$; Day: $F(6,108)=2.08$, ns; Sex $\times$ Day: $F(6,108)=4.24$, $p<0.05$). However, among saline self-administering rats, female rats overall had higher body temperatures, but both males' and females' daily body temperatures

decreased in a similar pattern (Saline- Sex: $F(1,20)=9.71$, $p<0.05$; Day: $F(6,120)=10.60$, $p<0.05$; Sex $\times$ Day: $F(6,120)=1.46$, ns).

To assess the effects of METH self-administration, striatal DAT and hippocampal BDNF immunoreactivity were evaluated. METH self-administration decreased DAT immunoreactivity in the striatum (Drug: $F(1,37)=7.43$, $p<0.05$; Figure 2A). However, there was no significant effect of sex ($F(1,37)=0.02$, ns) or Sex $\times$ Day interaction ($F(1,37)=0.65$, ns). It should be noted that the magnitude of the change was greater in females than males that self-administered METH (44% decrease in females versus 25% decrease in males compared to sex-matched controls). Lastly, hippocampal BDNF immunoreactivity was significantly increased in METH self-administering males but not METH self-administering females (Sex $\times$ Day: $F(1,38)=5.59$, $p<0.05$; Figure 2A). No significant effect of Sex or Drug was found (Sex: $F(1,38)=1.16$, ns; Drug: $F(1,38)=3.38$, $p=0.07$).

4.0 Discussion

The current study investigated the potential sex-differences in the neurochemical effects of METH self-administration. Results revealed similar METH intake between male and female rats, but females and METH rats had higher body temperatures. In both sexes, METH self-administration reduced striatal DAT immunoreactivity. However, only male rats that self-administered METH had elevated hippocampal BDNF levels.

In previous self-administration studies, female rats acquired METH self-administration more readily and/or self-administered more METH on a mg/kg basis (Kucerrova et al., 2009; Reichel et al., 2012; Roth and Carroll, 2004). These findings are in contrast to the current study. Likely differences in self-administration protocols such as infusion doses or access accounts for these differences. Because of the relative high drug intake and elevated body temperatures, the current study may better model that of human METH users with high drug intake that may lead to toxicity, whereas other paradigms may model METH users with low to moderate drug intake. Finally, the current protocol resulted in equal METH intake on a mg/kg bases between the sexes; therefore, it was chosen for ease of interpretation of the neurochemical results.

Female rats that self-administered METH had the highest body temperatures following self-administration and were closer to temperatures observed in neurotoxic METH exposures (McFadden et al., 2012A). Hyperthermia is a known mediator of METH-induced toxicity (Bowyer et al., 1994; Matsumoto et al., 2014), therefore may contribute to neurochemical changes. Despite similar METH intake, female rats that self-administered METH had a sensitization in body temperatures whereas male rats that self-administered METH had stable body temperatures across the seven sessions. Of note, increased hyperthermia to METH is also seen following chronic unpredictable stress (Matuszewich and Yamamoto, 2004), raising the possibility that sex-differences in the response of the hypothalamic-pituitary-adrenal axis to METH may develop over the course of self-administration. However, among saline groups, body temperatures decreased in a similar pattern between the sexes, suggesting a habituation to the daily procedures. Habituation of a physiological response to repetitive procedures are also observed in humans (Epstein et al., 1992). These

changes in the physiological response to METH may contribute to sex-differences in neurochemical changes observed in the brain.

Interestingly, sex-differences existed in the hippocampus. Consistent with previous findings, BDNF levels were elevated in the hippocampus of METH self-administrating male rats (Krasnova et al., 2013; Galinato et al., 2015; McFadden et al., 2014). Of note Galinato and colleagues found these changes to be accompanied by the lowering in the pro-apoptotic protein Bax and the increasing the anti-apoptotic protein Bcl-2 further suggesting that these changes may mitigate the toxicity induced by METH self-administration (Galinato et al., 2015). However, in the current study, female rats that self-administered METH did not have changes in BDNF levels. Of clinical relevance, male recently abstinent human psychostimulant users (cocaine or METH users) had higher serum BDNF levels than females when the number of abstinence days was controlled for (Hilburn et al., 2011). Further, recently abstinent female METH users but not males had decreased hippocampal volumes compared to sex-matched controls (Du et al., 2015). Perhaps prolonged use of METH coupled with a lack of changes in BDNF may contribute to lower hippocampal volumes.

The increase in body temperatures paired with the lack of changes in BDNF in female rats that self-administered METH suggest that they may be more vulnerable to the toxic effects of the drug. Indeed, the decrease in DAT immunoreactivity in the striatum was nearly twice that of male rats that self-administered METH despite taking similar amounts of METH. Epidemiology findings also suggest that female METH/amphetamine users are nearly 7 times more likely to develop Parkinson's Disease, which is associated with a loss of dopaminergic neuronal terminals in the striatum, as compared to male METH/amphetamine users who are 1.7 times more likely to develop the disease compared to sex-matched controls (Curtin et al., 2015). Further, female psychostimulant users had reduced grey matter volumes in multiple brain regions following prolonged abstinence while male psychostimulant users had few changes compared to sex-matched controls (Regner et al., 2015). Sex-differences in factors such as trophic factors may contribute to the sex-differences observed in clinical epidemiology and imaging studies, and thus warrant further investigation.

Overall, the current study investigated the potential sex-differences in the neurochemical changes following extended access METH self-administration. Despite similar METH intake, sex-differences existed in the effects of self-administration. These differences may render females to be more susceptible to the degenerative effects of METH.

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Highlights

- Male and female rats self-administered similar amounts of methamphetamine (METH)
- METH reduced striatal dopamine transporter immunoreactivity
- Only male METH self-administering rats had elevated hippocampal brain-derived neurotrophic factor (BDNF) levels

A.

B.

C.

Figure 1.

Rats were allowed to self-administer for 7 days and were sacrificed 1 hour after the last session. Active lever presses (Panel A), daily METH intake (Panel B) and body temperatures (Panel C) were recorded after each session. ** $p < 0.05$ METH vs. Saline. @ $p < 0.05$ from D1 to D7. ^ $p < 0.05$ Male vs. Female

A.

B.

Figure 2.

Striatal DAT (Panel A) and hippocampal BDNF (Panel B) immunoreactivity were assessed via western blotting following self-administration. * $p < 0.05$ METH Male vs. all other groups depicted. ** $p < 0.05$ METH vs. Saline