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The Persistent Neurotoxic Effects of Methamphetamine on Dopaminergic and Serotonergic Markers in Male and Female Rats

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Abstract

Objective: Methamphetamine (METH) is a highly addictive substance abused world-wide in both males and females. Preclinical studies in male rodents suggest that large-dose exposure to METH can lead to persistent neurotoxic consequences to various brain regions. However, little research has focused on the potential role of sex in the neurotoxic consequences of METH exposure.

Methods: The current study exposed male and female rats to large-doses of METH (4 injections of 7.5 mg/kg) or saline. Hyperthermia was promoted in the females exposed to METH such that similar hyperthermia occurred in males and females. Rats were sacrificed 8 d later and neurochemical changes were assessed in the striatum, hippocampus, frontal cortex and olfactory bulbs.

Results: Results revealed that male and female rats exposed to METH had similar decreases in dopamine (DA) transporter (DAT) immunoreactivity in the striatum, serotonin (5-HT) content and 5-HT transporter (SERT) function in the hippocampus, and 5-HT content in the frontal cortex. However, female rats exposed to METH had greater decreases in 5-HT content in the olfactory bulbs compared to sex-matched controls while male rats exposed to METH did not significantly differ from sex-matched controls.

Conclusions: These findings suggest that when similar hyperthermia is maintained between male and female rats exposed to METH, the neurotoxic effects of METH were similar in some, but not all brain regions.

Keywords: Methamphetamine; Sex-differences; Striatum; Hippocampus; Frontal cortex; Olfactory bulbs

Abbreviations:

DA: Dopamine; DAT: Dopamine Transporter; METH: Methamphetamine; 5-HT: Serotonin; SERT: Serotonin Transporter

Introduction

Methamphetamine (METH) is a highly addictive drug that leads to devastating consequences including increases in the prevalence of psychiatric symptoms, health problems, violence, criminal behaviour and death [1,2]. Of importance, clinical studies have shown that METH is abused by both males and females [3-8] but few preclinical studies have investigated potential sex-differences in the toxic effects of this drug in various brain regions. Preclinical data suggest that high doses of METH can lead to persistent serotonergic and dopaminergic deficits including decreases in dopamine (DA) transporters (DAT) function and/or immune reactivity, and DA and serotonin (5-HT) tissue content within the striatum of male rodents [9-14]. METH also damages other brain regions including the hippocampus, frontal cortex and olfactory bulbs [14-21]. Specifically, high doses of METH will lead to depletions in 5-HT content within the hippocampus and frontal cortex [13,14,16-20], as well as decreases in DA and/or 5-HT content within the olfactory bulbs [15,21].

Hyperthermia is one of the most common symptoms of an overdose reported in METH users [22]. Preclinical studies have suggested that hyperthermia leads to increased toxicity in a variety of brain regions including the striatum, hippocampus, and amygdala as well as the blood-brain barrier in males [10,23,24]. However, female mice also have reduced hyperthermia and toxicity following METH compared to males [25,26]. A large single injection of METH (40 mg/kg) leads to smaller DA depletions, as well as other markers of toxicity, in the striatum of female mice compared to males [25-27]. However, when similar hyperthermia was maintained between male and female rats during a multiple METH exposure, similar decreases in DA and 5-HT content were found within the striatum [28]. These findings suggest that hyperthermia may mediate the attenuation in deficits within the striatum induced by METH in females. However, little is known if sex-differences exist in other brain regions following neurotoxic METH exposures.

The purpose of this study was to examine if sex-differences exist in the persistent effects of multiple METH exposures in various brain regions. Results revealed that when similar hyperthermia was maintained between male and female METH-exposed rats, similar deficient were found between the sexes in the striatum, hippocampus, and frontal cortex. However, in the olfactory bulbs, female rats exposed to METH had significant decreases in 5-HT content compared to saline females while METH-exposed males had similar 5-HT content compared to sex-matched controls.

Methods

Animals

Adult female and male Sprague-Dawley rats (Charles River Laboratories, Portage, MI; postnatal day 75) were housed 2-3 rats/cage in a transparent plastic cage. Water and food were available in their home cage ad libitum. Rats were maintained under a 14:10 h light/dark cycle. Animals were sacrificed by 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.

METH challenge

Rats were challenged with 4 injections of METH (7.5 mg/kg/injection METH expressed as free-base and generously supplied by the National Institute on Drug Abuse, National Institute of Health, Bethesda, MD; 2 h interval) or saline (1 ml/kg/injection). Rectal temperatures were measured by using a digital thermometer (Physiotemp Instruments, Clifton, NJ) approximately 30 and 90 min after each METH injection. Hyperthermia in female rats exposed to METH was promoted by maintaining them in a warmer environment compared to males. Animals were sacrificed 8 d after the binge exposure.

Synaptosomal [^{3}H]5-HT uptake

[^{3}H]5-HT uptake was determined using the hippocampal synaptosomal preparation described previously [13]. In brief, synaptosomes were prepared by homogenizing freshly dissected hippocampal tissue in 0.32 M ice-cold sucrose buffer (pH 7.4) and were centrifuged (800 xg for12 min at 4°C). The supernatants were centrifuged (22,000 xg, 15 min, 4°C) and the resulting pellets were resuspended in ice-cold assay buffer (in mM: 126 NaCl, 4.8 KCl, 1.3 $CaCl_2$, 16 sodium phosphate, 1.4 $MgSO_4$, 11 glucose and 1 ascorbic acid; pH 7.4) and 1 μM pargyline. Samples were incubated for 10 min at 37°C and the assay was initiated by the addition of [^{3}H]5-HT (5 nM final concentration). Following incubation for 3 min, samples were placed on ice to stop the reaction and were then filtered through GF/B filters (Whatman, Florham Park, NJ) soaked previously in 0.05% polyethylenimine. Filters were rapidly washed three times with 3 mL of ice-cold 0.32 M sucrose buffer using a filtering manifold (Brandel, Gaithersburg, MD). Nonspecific values were determined in the presence of 10 μM fluoxetine. Radioactivity trapped in filters was counted using a liquid scintillation counter. Protein concentrations were determined using the Bio-Rad Protein Assay (Bio-Rad Laboratories Inc., Hercules, CA).

Western blotting

Striatal synaptosomes were prepared as described above by homogenizing freshly dissected striatum tissue. Equal quantities of protein (6 μg) of striatal synaptosomes were loaded into each well of a 4 to 12% NuPAGE Novex Bis-Tris Midi gradient gel (Invitrogen, Carlsbad, CA) and were electrophoresed using a XCell4 Surelock Midi-cell (Invitrogen). Samples were then transferred to polyvinylidene difluoride hybridization transfer membrane (PerkinElmer Life and Analytical Sciences, Waltham, MA). Membranes were blocked for 45 mins with Starting Block Blocking Buffer (Pierce Chemical, Rockford, IL) and incubated overnight at 4°C with an anti-DAT polyclonal antibody (C-20; 1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA). The membranes were washed five times in Tris-buffered saline with Tween (250 mM NaCl, 50 mM Tris, pH 7.4, and 0.05% Tween 20) and incubated for 1 h with a horseradish peroxidase-conjugated secondary antibody (BioSource International, Camarillo, CA). After five washes in Tris-buffered saline with Tween, the bands were visualized using Western Lightning Chemiluminescence Reagents Plus (PerkinElmer Life and Analytical Sciences) and were quantified by densitometry using a FluorChem SP Imaging System (Alpha Innotech, San Leandro, CA). Membranes were then stripped with Restore Western Blot Stripping Buffer (Thermo Scientific, USA) and reprobed with anti-β-Actin primary antibody (12E5, Cell Signaling Technology, USA). DAT immunoreactivity was then normalized to β-actin immunoreactivity. Protein concentrations were determined using the Bradford Protein Assay.

Tissue monoamine content

The anterior portion of the left striatum, hippocampus, frontal cortex, or olfactory bulb was sonicated for 3 to 5 s in 0.25, 0.5, 0.5, or 0.75 ml of tissue buffer respectively (0.1 M phosphate/citrate buffer, pH 2.5, containing 10% methanol) and prepared as described previously [13]. Fifty microliters was injected onto a partisphere C-18 reverse-phase analytical column (5 μm spheres; 250 × 4.6 mm, Whatman, Clifton, NJ). Mobile phase consisted of 0.05 M sodium phosphate, 0.03 M citrate buffer, 0.1 M EDTA, 0.035% sodium octylsulfate, and 20% methanol (pH 2.8; flow rate 0.75 ml/min). Monoamines were detected by using an ampherometric electrochemical detector with the working electrode potential set at +0.73 V relative to an Ag^{2+}/AgCl reference electrode. Protein concentrations were determined using the Bradford Protein Assay.

Statistical analysis

Statistical analysis was conducted in Graph Pad Prism (La Jolla, CA). Statistical analyses among groups were conducted using an analysis of variance (ANOVA) followed by Newman-Keuls posthoc analyses. The data represent means ± standard error of the mean (S.E.M.) of 6-9 rats/group.

Results

During the multiple METH exposure, similar hyperthermia was maintained in male and female rats exposed to METH except at 30 min past the third injection of METH (Time x Treatment interaction: $F(24, 232)=9.68$, $p<0.05$; Figure 1A).

Animals were sacrificed 8 d after this METH exposure. METH exposure resulted in similar reductions in DA content ($F(1,29)=50.32$, $p<0.05$; Table 1) and DAT immunoreactivity ($F(1,29)=19.20$, $p<0.05$; Table 1) within the striatum in male and female rats when hyperthermia was maintained. No significant sex-differences or interactions were observed (DA content: Sex: $F(1,29)=0.28$, ns; Drug × Sex: $F(1,29)=2.73$, $p=0.11$; DAT Immunoreactivity- Sex: $F(1,29)=0.58$, ns; Drug × Sex: $F(1,29)=0.94$, ns). Serotonin content in the olfactory bulb was significantly reduced by METH ($F(1,28)=13.49$, $p<0.05$; Figure 1B). Of note, the Sex x Drug interaction approached significance ($F(1,28)=3.26$, $p=0.08$).

Region	Transmitter/Transporter	Saline Male	METH Male	Saline Female	METH Female
Striatum	DA (pg/ µg protein)	112.1 ± 4.8	36.2 ± 9.2*	102.4 ± 5.8	55.2 ± 11.8*
Hippocampus	5-HT (pg/ µg protein)	1.94 ± 0.08	1.18 ± 0.08*	1.97 ± 0.10	1.11 ± 0.12*
Frontal Cortex	5-HT (pg/ µg protein)	6.06 ± 0.34	3.59 ± 0.52*	7.24 ± 0.44	3.32 ± 0.48*
Striatum	DAT immunoreactivity/ β-Actin immunoreactivity	0.95 ± 0.26	0.17 ± 0.06*	0.70 ± 0.12	0.20 ± 0.05*
Hippocampus	SERT function [3H] 5-HT Uptake (fmol/ µg protein)	1.08 ± 0.04	0.42 ± 0.09*	1.12 ± 0.08	0.36 ± 0.04*

Table 1: Monoamine content and Monoamine Transporter. Male and female rats were either exposed to METH (4 injections of 7.5 mg/kg, 2 h intervals) or saline and were sacrificed 8 d later. Monoamine content was assessed in the striatum, hippocampus, and frontal cortex. Transporters were assessed by western blotting (striatal DAT) or [3H]5-HT uptake (hippocampus SERT). *p<0.05 Saline *vs.* METH.

Similar deficits in hippocampal SERT function ($F(1,25)=81.70$, $p<0.05$; Table 1) were found in male and female rats treated with METH. Additionally, similar decreases in hippocampal 5-HT content were found ($F(1,29)=68.54$, $p<0.05$; Table 1). No significant sex-differences or interactions were observed (SERT- Sex: $F(1,25)=0.02$, ns; Sex × Drug: $F(1,25)=0.55$, ns; 5-HT content: Sex: $F(1,29)=0.03$, ns; Sex × Drug: $F(1,29)=0.26$, ns). In the frontal cortex, similar METH-induced depletions 5-HT content was found ($F(1,29)=49.06$, $p<0.05$). No significant effect of Sex or Sex × Drug interactions were found (Sex: $F(1,29)=1.01$, ns; Sex × Drug: $F(1,29)=2.51$, $p=0.12$).

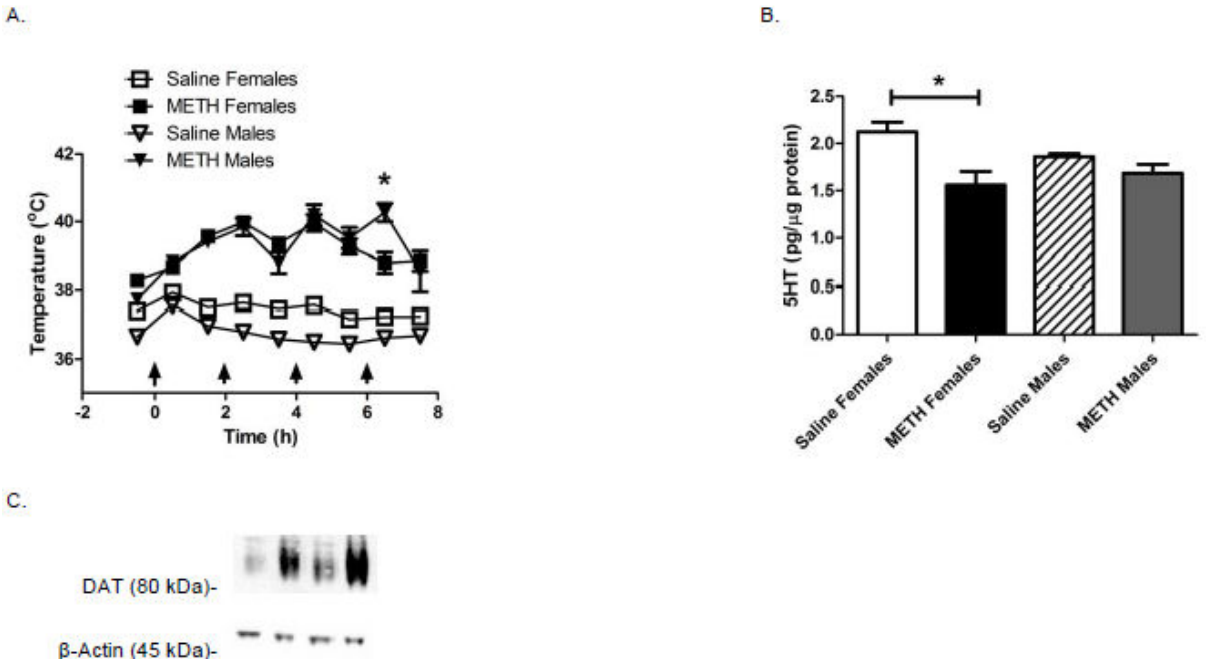

Figure 1: Male and female rats were given METH (4 injections of 7.5 mg/kg, 2 h intervals) or saline and hyperthermia was assessed (Panel A). Animals were then sacrificed 8 d later and 5-HT content was assessed in the olfactory bulb (Panel B). Representative western blot of DAT and β-Actin immunoreactivity of METH Female, Saline Female, METH Male and Saline Male groups (Left to Right; Panel C). * p<0.05 METH Males *vs.* METH Females, ** p<0.05 Saline Females *vs.* METH Females.

A one-way ANOVA revealed that METH Females had significantly lower 5-HT content compared to Saline Females ($F(3,28)=5.72$,

p<0.05). However, METH Males did not significantly differ from Saline Males. No significant effect of Sex in olfactory bulb 5-HT content was found ($F(1,28)=0.01$, ns).

Discussion

The current study investigated sex-differences in the neurotoxic effects of large-dose METH exposures when similar hyperthermia was maintained between the sexes. While maintaining similar hyperthermia between the sexes during the METH exposure mitigated many of the sex-differences in the neurotoxic consequences of METH, some sex-differences persisted. Female rats exposed to METH had a greater loss in 5-HT content within the olfactory bulbs compared to sex-matched controls than male rats. However, similar decreases in SERT function and 5-HT content were seen between male and female rats exposed to METH in the hippocampus. Further, similar depletions frontal cortex 5-HT content was also observed between the sexes following METH. Lastly, striatal DAT depletions following METH were similar between the sexes.

These findings are in agreement with past findings suggesting that hyperthermia may play an important role in sex-differences resulting from large-dose exposures to METH [28]. Because female rats weigh significantly less than age-matched male rats (approximately 2/3 that of males at postnatal day 75; Charles River Laboratories), it can be expected that unless efforts are made to promote hyperthermia, females will have reduced hyperthermia compared to males. To counteract this, in the current study female rats were exposed to METH in a warm environment to promote equal hyperthermia. When equal hyperthermia was promoted, females had similar persistent neurotoxic effects of METH in many, but not all brain regions measured. The current study suggests that disparities in sex-differences findings following large doses of METH may be due to sex-differences in hyperthermia.

Consistent with these findings is that METH-induced 5-HT depletions occurred only in hyper thermic mice maintained in warm environments [10]. Promoting hyperthermia has been shown to increase the formation of oxidative species and the degeneration of the blood-brain barrier [10,29]. This may have contributed to similar toxic effects of METH within the hippocampus and frontal cortex of male and female rats in the current study. It should be noted that although sex-differences in decreases in striatal DA content did not reach significance, the pattern of decreases was consistent with previous work showing attenuated METH-induced decreases in females (Females: 46.1% METH-induced decreases *vs.* Male: 67.7% METH-induced decreases compared to sex-matched controls) [25-27]. These findings suggest that hyperthermia may not be the only factor contributing to sex-differences in the effects of METH.

Other factors may contribute to these findings including sex-differences in the metabolism of METH. Females more slowly metabolize METH than males [30,31]. These sex-differences in metabolism combined with the repeated large doses of METH may have leads to prolonged exposure to METH in female rats and therefore, similar or greater toxicity in serotonergic markers in the frontal cortex, hippocampus, and olfactory bulbs when hyperthermia was promoted.

Female rats exposed to METH had significant reductions in olfactory bulb 5-HT content compared to sex-matched controls while males did not. Of importance, the olfactory bulb is thought to play an important role in a variety of behaviors. Serotonin in the olfactory bulb is an important modulator in odor input and early stage processing of odors [32]. Of clinical relevance, impairments in olfactation is one of the first symptoms in Parkinson's disease [33]; a disease also characterized by a significant loss of dopaminergic terminals in the striatum [34]. Recent clinical findings suggest that females who abuse METH and/or amphetamine have a greater risk of developing Parkinson's disease compared to their male counterparts [35]. The damage to the olfactory bulbs and striatum may suggest that female rats, when hyperthermia is promoted, may better model some aspects of Parkinson's disease. Future studies will further examine if these sex-specific changes in the olfactory bulbs result in impairments in symptoms consistent with Parkinson's Disease following exposure to a neurotoxic METH regimen.

Recently, the National Institute of Health has sought to include sex as a variable in preclinical studies investigating the effects of drugs [36]. The present study extended previous works investigating sex-differences the neurotoxic effects of METH by investigating changes in various brain regions affected by METH in females. Overall, maintaining similar hyperthermia between male and female rats reduced many but not all of the sex-differences in the persistent neurotoxic consequences of METH. Despite efforts to produce equal toxicity in males and females, sex-differences were still observed in the current study, thus illustrating the importance of including sex in studies investigating METH.

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