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Brief Report

BRIEF REPORT

Behavioral and Serotonergic Changes in the Frontal Cortex Following Methamphetamine Self-Administration

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Abstract

Background: Methamphetamine use is associated with a variety of negative health outcomes, including psychosis. The frontal cortex serotonin receptors are thought to contribute to psychosis-like behaviors. This study investigated changes in serotonergic markers in the frontal cortex following methamphetamine self-administration and hallucinogenic drug-induced behavior.
Methods: Consistent with previously published studies, freely cycling male and female rats were allowed to self-administer methamphetamine (males: 0.12 mg/infusion; females: 0.09 mg/infusion) or saline (10 µL) for 7 days. On the day following self-administration or following 10 days of extinction training, animals were given the serotonin 2A/2C agonist, 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (2 mg/kg, i.p.), and head twitches were analyzed. Autoradiography was also used to assess serotonin receptors and transporters in the frontal cortex following self-administration.
Results: Methamphetamine self-administration led to an increase in DOI-induced head-twitch behavior compared to saline only on the day following self-administration. Increases in serotonin receptors in the orbitofrontal cortex and decreases in serotonin transporters in the orbitofrontal cortex and infralimbic cortex were observed following methamphetamine self-administration as assessed by autoradiography.
Conclusions: Methamphetamine self-administration was associated with serotonergic alterations in the frontal cortex, which may underlie behavioral changes related to methamphetamine-associated psychosis.

Keywords: females, methamphetamine, self-administration, serotonin-2 receptors

Introduction

Methamphetamine (METH) abuse is a serious worldwide health problem. Epidemiology studies suggest approximately 40% of METH users display psychiatric symptoms, including schizophrenia-like symptoms (Glasner-Edwards and Mooney, 2014). Recreational METH use was associated with a 2-fold increase in developing psychotic symptoms (McKetin et al., 2010). In many cases of METH-associated psychosis, symptoms resolve soon after abstinence, but a smaller subset of patients have symptoms that persist after continued abstinence (Hsieh et al., 2014). In approximately 30% of cases of METH-associated psychosis, symptoms persisted for up to 6 months, whereas 10% to 25% of cases had symptoms that persisted for more than 6 months (Hsieh et al., 2014). Understanding the underlying cause of these psychiatric symptoms is imperative to understanding METH-associated psychosis and developing effective treatments.

Hallucinations are one symptom of METH-associated psychosis (Zarrabi et al., 2016), which may be due to an increase in serotonin (5-HT) activity (Müller et al., 2015). Previous research

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suggests the 5-HT2 receptors play an important role in drug-associated hallucinations (Smith et al., 2014). Drugs that stimulate the 5-HT2 receptors such as the psychedelics or 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI) produce hallucinations in humans and head-twitch behaviors in rodents (Halberstadt and Geyer, 2013). In humans, blockade of the 5-HT2 receptors with the antagonist ketanserin reduces the subjective effects of lysergic acid diethylamide (Preller et al., 2017). Further, many atypical antipsychotics work in part as an inverse agonist or antagonist to the 5-HT2A receptor (Bozymski et al., 2017), which may in turn reduce psychosis and hallucination-like symptoms. These findings suggest that the serotonergic system may play an important role in hallucinations.

Previously, we reported that METH self-administration in male rats decreases 5-HT content in the frontal cortex (McFadden et al., 2013). Previous research suggests the 5-HT2A receptor expression is inversely related to 5-HT levels or 5-HT transporter (SERT) densities in the frontal cortex (Cahir et al., 2007; Urban et al., 2012). The decrease in 5-HT content after METH self-administration may lead to alterations in 5-HT2 receptors in the frontal cortex and hallucinogenic drug-associated behaviors following METH use.

The purpose of this study was to investigate changes in hallucinogenic drug-induced behavior following METH self-administration in male and female rats. Given prior studies in humans suggesting METH use may lead to drug-associated psychosis, the goals of this study were to: (1) establish if prior METH self-administration in rats would lead to behavioral changes using a previously validated model of hallucinogenic drug-associated behaviors, DOI-induced head twitches (González-Maeso et al., 2007; Fantegrossi et al., 2010); (2) establish if these changes persisted following extinction training; (3) establish if these changes differed by sex in freely cycling animals (i.e., neither castrated nor ovariectomized animals); and (4) gain insight into the possible changes in the cortex that may be associated with changes in hallucinogenic drug-associated behaviors. To test this, rats were allowed to self-administer METH or saline for 7 days. On the day following self-administration or following 10 days of extinction training, animals were given the 5-HT2A/2C agonist, DOI, and head twitches were analyzed. To understand the neurochemical changes underlying these responses, autoradiography was used to assess changes in the 5-HT2 and receptor SERT in the frontal cortex. Findings suggest METH self-administration was associated with an increase in 5-HT2 receptors and a decrease in SERT in the orbital frontal cortex (OFC),which may underlie behavioral changes related to METH-associated psychosis.

Methods

Animals

Adult male and female Sprague-Dawley rats (approximately 56 days old; Charles River Laboratories or Invigo) were housed 2 rats/cage. Following surgery, each rat was individually housed in a transparent plastic cage. Water was available in their home cage ad libitum. During food training, rats were food restricted such that no rat dropped below 90% of their starting body weight. Rats were maintained under the same light/dark cycle in the animal facility and in the operant chambers. Females were freely cycling. Animals were killed by decapitation. All experiments were approved by the University of Utah's or the University of South Dakota's Institutional Animal Care and Use Committee, in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Food Training, Self-Administration, and Extinction Training

Food training, self-administration, and extinction training occurred in an operant chamber (Coulbourn Instruments) as described previously (Johansen et al., 2017). Prior to catheter surgery rats received 4 (14 h/night) food training sessions during which pressing the active lever resulted in a 45-mg food pellet. Rats underwent 7 days of self-administration (8 h/session; FR1; male: 0.12 mg/infusion or female: 0.09 mg/infusion racemic-METH expressed as free-base; or saline) during the light cycle. For each active lever press, an infusion pump delivered 10 µL of METH or saline over a 5-second duration. During this period, both levers were retracted. Following the infusion, the levers remained retracted for an additional 20 seconds. Pressing the inactive lever resulted in no programmed consequences, although it was recorded. Each animal's daily METH intake was normalized to their daily body weight (mg/kg). A subset of animals continued to receive 10 days of extinction training (2 h/d). Animals were tethered and placed in the operant chambers as during self-administration, but lever presses resulted in no consequence, although they were recorded.

DOI-Induced Behavior

Animals underwent behavioral testing on the day following self-administration or after 10 days of extinction training. Rats received a 2-mg/kg injection (i.p.) of DOI. The dose of DOI was carefully chosen based on previous work suggesting it produced robust head twitch behavior (González-Maeso et al., 2007; Fantegrossi et al., 2010) and based on preliminary studies in our laboratory suggesting it robustly increased head twitches in both sexes. Previous studies have found DOI has a preferential binding affinity to the 5-HT2A receptor (5-HT2A Ki: 0.7 nM; 5-HT2C Ki: 2.4 nM; Nelson et al., 1999). Animals were then placed in a clean cage, recorded for 30 minutes for further assessment of head twitch behavior, and returned to their home cage. Head twitches were assessed by a blinded coder.

Autoradiography

Rats were killed 1 hour after the last self-administration session via rapid decapitation to avoid anesthesia-induced alterations in neurotransmitters (see Kalén et al., 1988; Tao et al., 1994). Brains were removed, rapidly frozen on dry ice, and stored at -80°C until sliced. Coronal slices (12 µM) of the frontal cortex were sectioned on the cryostat. To assess 5-HT2 receptors in the frontal cortex, [3H]-ketanserin was used as described in Preece et al., 2004. Briefly, slides were incubated in 2 nM of [3H]-ketanserin containing 100 nM prazosin for 15 minutes. Nonspecific binding was determined by the addition of M100907 (1 µM) to the [3H]-ketanserin buffer. Following 3 washes and dryings, slides were placed on film and developed after 12 weeks of exposure.

[125 I]-RTI-55 was used to assess SERT densities as described in Furlong et al., 2016. Briefly, slides were incubated for 2 hours in 25 pmol of [125 I]-RTI-55 containing 200 nM GBR12935. Fluoxetine (100 nM) was added to the [125 I]-RTI-55 to assess nonspecific binding. Following 3 washes and dryings, slides were placed on a film and developed after a 15-hour exposure. Autoradiographic images were captured and analyzed in ImageJ by blinded experimenters. Densitometric analysis was used to

determine average density values of the prelimbic (PrL), infralimbic (IL), and OFC across 2 sections (between +2.7 and 4.0 mm from bregma). Samples with tears in the region of interest were excluded from analyses.

Statistical Analysis

Statistical analysis was conducted in SAS Studio or GraphPad Prism 7. Statistical analyses among groups were conducted using a 2-way ANOVA or repeated-measures ANOVA followed by Tukey's posthoc analyses. Posthoc analyses can be found in the supplemental information. The data represent means ± SEM of 4 to 9 rats/group. Only animals with patient catheters were included in analysis. Only METH rats that met the criteria for high pressers (1: average of >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 for the autoradiography experiments and one male for the behavioral experiments. An additional 4 males were excluded due to equipment failure during one self-administration session.

Results

In all cases of self-administration, METH animals escalated intake over the course of self-administration [Behavioral No Extinction: $F(6,72) = 45.72$, $P < .05$, Figure 1A; Behavioral Extinction: $F(6,72) = 30.30$, $P < .05$, Figure 1B]. No sex differences were observed in METH intake [Behavioral No Extinction: $F(1,72) = 0.79$, ns; Behavioral Extinction: $F(1,72) = 0.03$, ns] nor did sex interact with day [Behavioral No Extinction: $F(6,72) = 0.26$, ns; Behavioral Extinction: $F(6,72) = 0.16$, ns]. Self-administration for the autoradiography findings has been previously published (see Figure 1 of Johansen et al., 2017) but followed a similar pattern.

Animals were treated with a 2-mg/kg (i.p.) injection of DOI, and head twitches were counted for 30 minutes following the injection. METH self-administering rats had a greater number of DOI-induced head twitches compared to saline self-administering rats when tested after the last self-administration session [Drug: $F(1,23) = 11.92$, $P < .05$; Drug x Sex: $F(1,23) = 0.04$, ns; Figure 1C]. Females also had a greater number of DOI-induced head twitches compared with males [$F(1,23) = 7.18$, $P < .05$]. When 10 days of extinction training were given following self-administration, METH and saline self-administering rats had a similar number of DOI-induced head twitches [Drug: $F(1,21) = 0.00$, ns; Drug × Sex: $F(1,21) = 1.37$, ns; Figure 1D]. However, sex differences were observed [Sex: $F(1,21) = 11.18$, $P < .05$].

5-HT2 receptors were altered in the frontal cortex of METH rats following self-administration as assessed by [3H]-ketanserin autoradiography (Supplemental Figure A). Because changes in head twitch behavior were not observed following extinction training, changes in the frontal cortex were not investigated following extinction training. Higher 5-HT2 receptors were observed

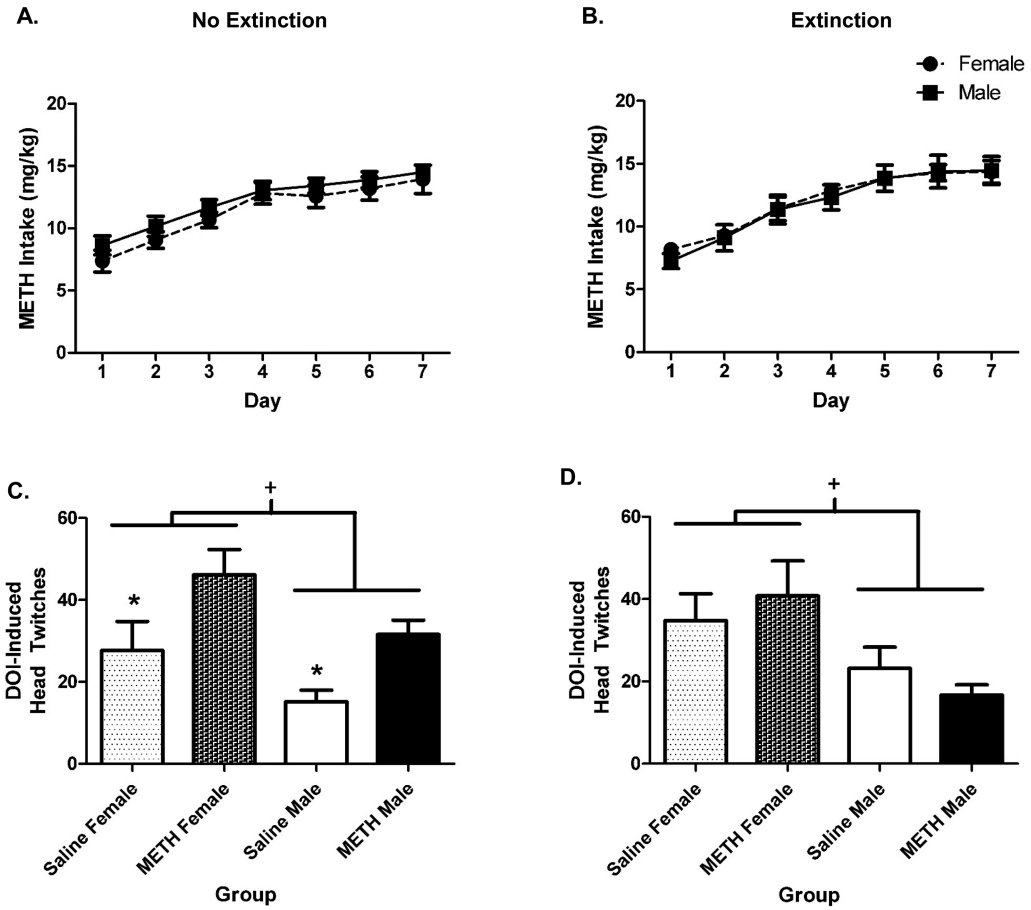

Figure 1. Methamphetamine (METH) intake and 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI)-induced changes in behavior. Animals were allowed to self-administer METH or saline for 7 days. METH intake (mg/kg) escalated over time but did not differ between the sexes in the animals tested immediately after self-administration (A) or following extinction training (B). Animals were injected with 2 mg/kg DOI. Head twitch behavior was quantified for 30 minutes following injection in animals tested after self-administration (C) or extinction training (D). (A, C) Saline Female: n = 6; METH Female: n = 7; Saline Male: n = 7; METH Male: n = 7. (B, D) Saline Female: n = 5; METH Female: n = 5; Saline Male: n = 6; METH Male: n = 9. *$P < .05$ METH vs Saline; +$P < .05$ Female vs Male.

in the OFC [Drug: F(1,38) = 13.08, $P < .05$], and a trend towards higher receptors in the PrL occurred [Drug: F(1,36) = 2.88, $P < .10$], but no differences were found in the IL [Drug: F(1,36) = 0.00, ns] in METH compared with saline self-administering rats (Table 1). No sex differences were noted [sex: OFC: F(1,38) = 3.24, $P = .08$; PrL: F(1,36) = 0.33, ns; IL: F(1,36) = 0.02, ns; Sex x Drug: OFC: F(1,38) = 0.46, ns; PrL: F(1,36) = 0.09, ns; IL:F(1,36) = 0.39, ns].

Serotonin transporters were also altered in the frontal cortex of METH rats following self-administration as assessed by [125 I]-RTI-55 autoradiography (Supplemental Figure B). Lower SERT in METH self-administering rats was observed in the OFC [F(1,29) = 4.67, $P < .05$] and IL [F(1,25) = 8.16, $P < .05$], but no statistical differences were found in the PrL [F(1,26) = 2.19, ns; Table 1]. No sex differences were noted [Sex: OFC: F(1,29) = 0.39, ns; PrL: F(1,26) = 2.86, ns; IL: F(1,25) = 0.25, ns], but a significant Sex × Drug interaction occurred in the IL, suggesting that these METH-induced decreases were specific to the males [IL: F(1,25) = 5.85, $P < .05$; OFC: F(1,29) = 2.79, ns; PrL: F(1,26) = 0.70, ns].

Discussion

Overall, our findings suggest that prior METH self-administration increases the responsiveness to a 5-HT2 agonist shortly after self-administration but not after extinction training, as evident by the behavioral responses to DOI. In separate animals, autoradiography was performed to assess changes in serotonergic markers in the frontal cortex when sacrificed shortly after the last self-administration session. Results revealed a decrease in SERT autoradiography and an increase in 5-HT2 receptor autoradiography in METH self-administering animals compared with saline animals in the OFC. These changes may contribute to the behavioral changes observed.

Changes to the 5-HT2 receptors in the frontal cortex may contribute to hallucinations associated with METH use. The self-administration of METH lead to an increase in DOI-induced head twitches compared to saline self-administering animals. In addition to the increase in head twitch behavior, an increase in 5-HT2 receptors in the OFC was observed. Because METH increases 5-HT activity rather than binding to specific 5-HT receptors (Müller et al., 2015), the less specific 5-HT2 agonist was used to more closely mimic that of METH. Although DOI and ketanserin both have a higher affinity for the 5-HT2A receptor compared with the 5-HT2C receptor (Nelson et al., 1999; Rashid et al., 2003), one limitation of this study is that these drugs bind to both 5-HT2 receptors. However, the changes observed in both behavior and autoradiography warrant the need for future studies to investigate the specific 5-HT2 receptor subtype underlying these changes.

Previous studies have investigated the pharmacology underlying drug-induced head twitch behavior. Studies suggest this head-twitch behavior is primarily mediated by the 5-HT2A receptor (Gonzalez-Maeso et al., 2007), but other receptors including the 5-HT2C receptor may also modulate this behavior (Fantegrossi et al., 2010). More specifically, cortical expression of the 5-HT2A receptor is necessary to induce head twitches by hallucinogenic drugs (González-Maeso et al., 2007). Moreover, this behavior may be mediated by stimulating heterocomplexes formed by the 5-HT2A and metabotropic glutamate-2 receptors (mGlu2), for mGlu2 knockout mice have reduced head twitch behavior (Moreno et al., 2011; Holloway et al., 2016). The increase in head twitch behavior in METH self-administering rats in the current study may not only be due to the slight increase in 5-HT2 receptors in the frontal cortex, but rather to an increase in the formation of 5-HT2A/mGlu2 heterocomplexes. Future studies are needed to investigate the formation of these complexes following METH self-administration.

Changes to 5-HT2 receptors were inversely related to changes in SERT in the OFC. Previous research suggests that reducing 5-HT content via dietary tryptophan depletion for 3 weeks leads to an increase in 5-HT2A receptors in the cortex but not striatum (Cahir et al., 2007). Further, chronic human MDMA users have reduced SERT availability and increased 5-HT2A receptor binding in the cortex (Urban et al., 2012). We speculate that the increase in 5-HT2 receptor autoradiography following self-administration may be associated with the decrease in SERT in the OFC and perhaps 5-HT content in the frontal cortex. Previous research in our laboratory suggests that 5-HT content is reduced in the frontal cortex following METH self-administration in males (McFadden et al., 2013). This may be due to a loss of serotonergic neuronal terminal integrity in the frontal cortex as reflected by the reduction in SERT, which in turn may lead to an upregulation in 5-HT2 receptors, especially in the OFC.

Females also had greater head twitch behavior compared with males regardless of self-administration group. This may be due to sex hormones. Estradiol benzoate replacement therapy in ovariectomized rats results in increases in 5-HT2A receptors in the frontal cortex (Sumner et al., 1999). Further, estradiol replacement therapy in postmenopausal women has been shown to increase 5-HT2A receptor binding in the frontal cortex (Kugaya et al., 2003). The sex differences observed in the current study may have been due to sex differences in estrogen levels. Although it was beyond the scope of the current study investigating METH-induced changes in and hallucinogenic drug-associated behaviors, future studies are warranted to investigate the influence of sex hormones on 5-HT2 receptor expression and behavioral pharmacology.

The behavioral changes induced by METH self-administration were not long lasting. This is consistent with clinical reports that in the majority of patients with METH-associated psychosis, these symptoms go into remission shortly after achieving abstinence from drug use (Zorick et al., 2010; Hsieh et al., 2014).

Table 1. Frontal Cortex Autoradiograph (% of Saline Male) in Animals Sacrificed 1 Hour after Self-Administration

Ligand	Region	Saline Male	METH Male	Saline Female	METH Female
[3H] Ketanserin	PrL#	100.00 ± 2.28 (10)	102.65 ± 1.99 (10)	100.52 ± 1.59 (11)	104.29 ± 1.60 (9)
	IL	100.00 ± 3.45 (10)	102.16 ± 2.66 (10)	101.52 ± 2.30 (11)	99.78 ± 4.11 (10)
	OFC*	100.00 ± 1.86 (11)	106.22 ± 1.92 (10)	102.37 ± 2.36 (11)	111.47 ± 2.26 (9)
[125 I] RTI-55	PrL	100.00 ± 1.53 (4)	87.59 ± 3.79 (9)	104.56 ± 5.83 (8)	101.13 ± 5.30 (9)
	IL*&	100.00 ± 1.88 (4)	80.96 ± 3.97 (8)	93.06 ± 3.33 (8)	91.48 ± 2.85 (9)
	OFC*	100.00 ± 3.56 (6)	89.72 ± 2.24 (10)	97.19 ± 2.55 (8)	95.87 ± 2.55 (9)

Mean ± SEM (n).

*$P < .05$ METH vs saline; #$P < .10$ METH vs saline; & $P < .05$ saline male vs METH male.

In an in-patient sample of METH users, the majority of psychotic symptoms resolved within 1 week of abstinence from the drug (Zorick et al., 2010). The results of the current study suggest that changes in 5-HT2-mediated behavior diminish quickly after abstinence from METH use. Other clinical studies suggest that up to 30% of individuals with METH-associated psychosis had symptoms that persisted up to 6 months (Hsieh et al., 2014), but it is unclear if these persisting symptoms are associated with the duration of drug use. Future studies can alter the duration of METH self-administration to assess if this leads to a subset of animals with persistent behavioral changes. Alternatively, it can be speculated that the persistence of METH-associated psychosis in the clinical population may reflect individuals with predispositions to psychosis or schizophrenia and METH use simply unmasked the symptoms of the disorder. Indeed, McKetin and colleagues (2016) observed that patients with persistent METH-induced psychosis may represent an etiologically distinct pathway from those with transient METH-induced psychosis. Future studies utilizing preclinical models of schizophrenia and METH self-administration may help interrogate the etiology of the persistence METH-induced psychosis.

Overall, the results of the current study suggest METH self-administration leads to changes in both the brain and behavior. Specifically, METH self-administration leads to an increase in DOI-induced head twitches 1 day after the end of self-administration but not following 10 days of extinction training. Additionally, 5-HT2 receptors and SERT were decreased in areas of the OFC following self-administration. These changes may underlie METH-associated psychosis observed in METH users. Further, 5-HT2 or 5-HT2A antagonist/inverse agonists may hold potential in reducing these symptoms in METH users.

Supplementary Materials

Supplementary data are available at *The International Journal of Neuropsychopharmacology* online.

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Statement of Interest

None.

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