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Prior methamphetamine self-administration attenuates the dopaminergic deficits caused by a subsequent methamphetamine exposure

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ABSTRACT

Others and we have reported that prior methamphetamine (METH) exposure attenuates the persistent striatal dopaminergic deficits caused by a subsequent high-dose "binge" METH exposure. The current study investigated intermediate neurochemical changes that may contribute to, or serve to predict, this resistance. Rats self-administered METH or saline for 7 d. On the following day (specifically, 16 h after the conclusion of the final METH self-administration session), rats received a binge exposure of METH or saline (so as to assess the impact of prior METH self-administration), or were sacrificed without a subsequent METH exposure (i.e., to assess the status of the rats at what would have been the initiation of the binge METH treatment). Results revealed that METH self-administration *per se* decreased striatal dopamine (DA) transporter (DAT) function and DA content, as assessed 16 h after the last self-administration session. Exposure to a binge METH treatment beginning at this 16-h time point decreased DAT function and DA content as assessed 1 h after the binge METH exposure: this effect on DA content (but not DAT function) was attenuated if rats previously self-administered METH. In contrast, 24 h after the binge METH treatment prior METH self-administration: 1) attenuated deficits in DA content, DAT function and vesicular monoamine transporter-2 function; and 2) prevented increases in glial fibrillary acidic protein and DAT complex immunoreactivity. These data suggest that changes 24 h, but not 1 h, after binge METH exposure are predictive of tolerance against the persistence of neurotoxic changes following binge METH exposures.

1. Introduction

Methamphetamine (METH) is a widely abused psychostimulant that can cause persistent alterations in monoaminergic neuronal function. Preclinical studies demonstrate that exposure to high-dose METH, administered to mimic some aspects of human "binge" usage, causes persistent dopaminergic deficits. METH-induced alterations in dopamine (DA) content, DA transporter (DAT) function, vesicular monoamine transporter-2 (VMAT2) function/distribution, and tyrosine hydroxylase (TH) activity 1–24 h post-treatment may contribute to these long-term deficits (Brennan et al., 2010; Chu et al., 2010; Eyerman and Yamamoto, 2007; Hadlock et al., 2009, 2010; Hotchkiss and Gibb, 1980; McFadden et al., 2012a). Increases in extracellular glutamate, reactivity species and oxidative stress formation, and glial activation are also thought to contribute to the dopaminergic deficits following binge METH exposure (for reviews see Krasnova and Cadet, 2009; Tata and Yamamoto, 2007).

Researchers have noted that administration of escalating doses or intake of METH models human patterns of METH use (Fischman and Schuster, 1974; Schmidt et al., 1985). Further, preclinical studies indicate that pretreatment with escalating doses of METH attenuates the deficits induced by a large neurotoxic binge exposure to METH (Schmidt et al., 1985), including persistent losses of DA and serotonin (5HT) content (Cadet et al., 2009; Hodges et al., 2011; Johnson-Davis et al., 2003; McFadden et al., 2012a,b; Segal et al., 2003), DAT function/immunoreactivity/binding (Belcher et al.,

Abbreviations: DOPAC, 3,4-dihydroxyphenylacetic acid; DA, dopamine; DAT, dopamine transporter; GFAP, glial fibrillary acidic protein; METH, methamphetamine; 5HT, serotonin; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter-2.

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2008; Krasnova et al., 2011; McFadden et al., 2012a,b; Segal et al., 2003), VMAT2 function (McFadden et al., 2011), and glial activation (McFadden et al., 2012a; Thomas et al., 2004). These studies are important since most individuals who abuse METH receive multiple exposures to the drug. However, relatively little is known of the mechanisms underlying the "neuroprotection" afforded by prior METH exposure.

Similar to the escalating-dose studies described above, our laboratory reported that prior METH self-administration reduced the persistent neurotoxic decreases in striatal DA content and DAT function caused by a subsequent binge METH exposure (McFadden et al., 2012a). These findings are of potential clinical relevance in that the resistance to binge-induced dopaminergic deficits caused by the repeated METH exposures may provide a model to explain why human METH abusers generally do not display dopaminergic deficits as great in magnitude as those resulting pre-clinically from a binge METH treatment, even after using large quantities of METH (McFadden et al., 2012a,b). Further, preclinical studies have suggested that contingent drug administration may lead to distinct neurochemical changes compared to non-contingent administration (Frankel et al., 2011; Hanson et al., 2012, 2013; Lominac et al., 2012; Stefanski et al., 2004).

Given the importance noted above of alterations 1–24 h post-METH treatment, the current study focused on such changes that may contribute to and/or predict this resistance to METH-induced deficits. Results revealed that METH self-administration *per se* decreased striatal DAT function and DA content, as assessed 16 h after the last self-administration session. Exposure to a binge METH treatment beginning at this 16-h time point decreased DAT function and DA content as assessed 1 h after the binge METH exposure: this effect on DA content, but not DAT function, was attenuated if rats were exposed previously to METH self-administration. In contrast, prior METH self-administration attenuated deficits in DA content, as well as DAT function and VMAT2 function as assessed 24 h after the binge treatment. Further, prior METH self-administration prevented increases in glial fibrillary acidic protein (GFAP) and DAT complex immunoreactivity compared to saline self-administrating/binge METH exposed rats at this 24 h time point. These findings suggest that striatal changes occurring 24 h after the binge exposure to METH are predictive of persistent deficits induced by a binge exposure to METH as previously reported (McFadden et al., 2012a).

2. Methods

2.1. Animals

Male Sprague–Dawley rats (275–300 g; Charles River Laboratories, Portage, MI) were housed four rats/cage (35 × 30 × 16 cm). Following surgery, each rat was individually housed in a transparent plastic cage (45 × 23 × 21 cm). 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 14:10 h light/dark cycle in the animal facility and in the operant chambers. 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 (Research Triangle Institute; Research Triangle Park, NC) was dissolved in 0.9% sterile saline, with the dose described as the free-base form. Ketamine (90 mg/kg; Hospira Inc., Lake Forest, IL, USA) and xylazine (7 mg/kg; Sigma–Aldrich, St. Louis, MO, USA) were used to anesthetize animals. The antibiotic cefazolin (10 mg/mL; Schein Pharmaceutical, Florham Park, NJ, USA) was dissolved in heparinized saline (63.33 U/mL; Sigma, St. Louis, MO, USA). Flunixin meglumine (1.1 mg/kg; MWI Veterinary Supply, Meridian, ID, USA) was used for post-surgery analgesia.

2.3. Food training and surgery

Food training and self-administration occurred in an operant chamber (30.5 cm × 25.5 cm × 30.5 cm; Coulbourn Instruments, Whitehall, PA, USA) as described in McFadden et al. (2012a). Prior to surgery, each rat was trained to press for a 45-mg food pellet during four overnight 14-h sessions. Following food training, rats were anesthetized and an indwelling catheter was implanted. The catheter was constructed as described previously (Frankel et al., 2011). Each rat received flunixin meglumine on the day of and following the surgery. Immediately following surgery and daily thereafter, each rat was infused with 0.1 mL of cefazolin followed by 0.05 mL of heparinized saline and heparinized glycerol. Catheter patency was confirmed by infusing 0.03 mL (20 mg/mL) of xylazine. The animals' food was reduced to 25 g the day before self-administration began. On all following days, animals were allowed to free feed.

2.4. Self-administration and METH challenge

Fig. 1 illustrates the time course of experiments. All rats underwent 7 d of self-administration (8 h/session; FR1; 0.12 mg/infusion METH or saline; with associated lever pressing presented as Supplemental Figure 1) during the light cycle in a room maintained at 29 ± 1 °C to promote lever pressing (Cornish et al., 2008). For each active lever press, an infusion pump connected to a liquid swivel (Coulbourn Instruments) delivered 10 μL of METH or saline per infusion over a 5-s duration through a polyethylene tube located within a spring leash (Coulbourn Instruments) tethered to the rat. During this period, both levers were retracted. Following the infusion, the levers remained retracted for an additional 20 s. The active lever was counterbalanced within each group. Pressing the inactive lever resulted in no programmed consequences although it was recorded. METH self-administering rats were only included in the analysis if they: 1) pressed an average of more than 10 active lever presses per d; and 2) the ratio of active/inactive lever presses was ≥2:1. These criteria were largely based upon those of Brennan et al. (2010). METH intake and body weight changes were similar between experiments and therefore representative pressing behavior and weights are illustrated in Fig. 2A and B. Animals were sacrificed 16 h after the end of the last self-administration session or received a binge of METH or saline as described below (Fig. 1).

Sixteen h after the end of the last self-administration session, rats were challenged with 4 injections of METH (7.5 mg/kg/injection; 2-h interval) or saline (1 mL/kg/injection). This time point was chosen based on research utilizing escalating doses of METH followed by a binge exposure (see Danaceau et al., 2007; O'Neil et al., 2006) and to replicate previous methods (McFadden et al., 2012a,b). Previous studies (McFadden et al., 2012a,b) have demonstrated that hyperthermia is attenuated during the binge exposure to METH in animals that had previously self-administered METH. To promote hyperthermia, METH self-administering rats challenged with METH (METH/METH) were maintained in a warm environment (25 °C). Rats that self-administered saline prior to the binge of METH (Saline/METH) were maintained in 22.5 °C environment to promote similar hyperthermia between METH/METH and Saline/METH groups. Previous research in our laboratory has shown that this higher ambient temperature permits binge METH-induced neurotoxicity that would have otherwise been attenuated by prior exposure to METH during development (see McFadden et al., 2011). Representative temperature data during the binge exposure to METH are provided in Fig. 2C. Animals were sacrificed 1 h or 24 h after the binge exposure (Fig. 1).

2.5. Tissue preparation

Tissue preparation was conducted as previously described (Hanson et al., 2009). Following decapitation, the striata were quickly dissected out and the right striatum was homogenized in ice-cold sucrose buffer (0.32 M sucrose, 3.8 mM NaH_2PO_4, and 12.7 mM Na_2HPO_4). The left striatum was quickly frozen on dry ice.

2.6. Plasmalemmal & vesicular [^{3}H]DA uptake assays

[^{3}H]DA uptake assays were conducted according to Johnson-Davis et al. (2004). For plasmalemmal uptake of [^{3}H]DA, striatal synaptosomes were prepared accordingly and resuspended in ice-cold Krebs' buffer (126 nM NaCl, 4.8 mM KCl, 1.3 mM $CaCl_2$, 16 mM sodium phosphate, 1.4 mM $MgSO_4$, 11 mM dextrose, 1 mM ascorbic acid, pH 7.4). Assay tubes containing 1.5 mg striatal tissue and 1 μM pargyline were incubated (3 min, 37 °C) with [^{3}H]DA (0.5 nM final concentration, Perkin Elmer,

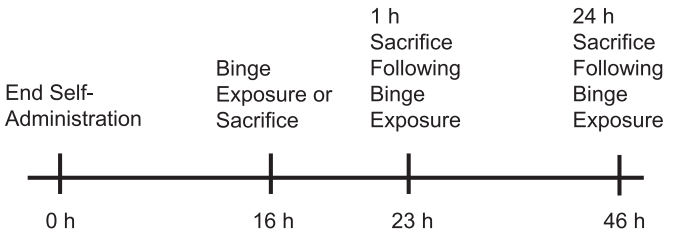

Fig. 1. Sacrifice times of rats in the manuscript. Animals were allowed to self-administer METH or Saline for 7 d. Sixteen hours after the last self-administration session rats were sacrificed or received a binge exposure to METH or Saline. Rats were sacrificed 1 h or 24 h after the binge exposure.