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Research report

Persistent behavioral and neurochemical sensitization to an acute injection of methamphetamine following unpredictable stress

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HIGHLIGHTS

- Stress increases methamphetamine's effects on locomotion.
- Stress increases methamphetamine-induced dopamine in the striatum.
- Stress increases methamphetamine-induced hyperthermia.
- Effects of stress are lasting.

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ABSTRACT

Prior research in humans and animals suggest that exposure to chronic stress alters the response to drugs of abuse, increasing vulnerability to drug addiction. Chronic unpredictable stress (CUS) has been shown to augment the increase of dopamine in the striatum when challenged with high doses of methamphetamine immediately following stress exposure, however it is not known whether this neurochemical stress-sensitization continues after the cessation of the stressors or if behavioral sensitization is also present. Therefore, the current study examined the immediate and delayed effects of CUS on methamphetamine-induced behaviors and striatal dopamine levels. Male rats were exposed to 10 days of CUS and then tested in either an open field box to assess locomotion or underwent in vivo microdialysis to measure striatal dopamine levels immediately following CUS or after a 1–2 week delay. All rats exposed to CUS showed a potentiated locomotor response immediately following an acute injection of 7.5 mg/kg methamphetamine compared to non-stressed control rats. Both groups of CUS rats also showed augmented dopamine release and rectal temperatures following methamphetamine with prolonged increases in the CUS rats tested after a delay. These results suggest that CUS increases the sensitivity of a rat to a single injection of methamphetamine and that the increased sensitivity persists for up to 2 weeks following the last stressor.

1. Introduction

Drug addiction to stimulants continues to be a serious health concern in the United States and worldwide. In the United States alone, 23.9 million individuals reported using illicit drugs with 1.2 million using non-medical stimulants [1]. Methamphetamine is a potent stimulant with long-term, damaging effects to the brain [2–4]. Approximately 5% of adults have reported using methamphetamine during their lifetime with chronic users showing changes to neural markers after extended abstinence [5,6]. Acutely, methamphetamine acts at monoamine terminals to release neurotransmitters and its rewarding and addictive properties are thought to be associated with dopamine release in several forebrain regions, including the ventral and dorsal striatum [2].

Prior exposure to stress may increase an individual's sensitivity to stimulants, leading to an increased vulnerability to substance use and addiction [for reviews see 7, 8, 9]. The increased sensitivity to stimulants following stress has been termed cross-sensitization and has been shown behaviorally through locomotor measures in open field tests. Rats exposed to repeated foot shock, restraint or social defeat stress show greater locomotion to a subsequent injection of cocaine or amphetamine [10–22]. Exposing rats to

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chronic unpredictable stress (CUS), where the stressors differ each day also has been shown to augment the increase in locomotor activity following an acute cocaine injection in some experimental procedures [23–25] but not under all conditions [10,24]. One variable that may influence the presence of cross-sensitization is the time period between the stress exposure and the stimulant injection. Some studies have found an increase in cocaine-stimulated locomotion when tested immediately after the end of the stress procedures [18,23,26,27], while others reported their effects after a delay of 4–14 days [21,28]. Currently, there are no published studies reporting whether exposure to unpredictable stress increases the behavioral effects of methamphetamine immediately or following a delay, despite its potent stimulatory effects in humans and rats [29–31]. Thus, we investigated whether exposure to chronic unpredictable stress would potentiate the behavioral effects of an acute injection of methamphetamine either immediately or 2 weeks following stress exposure.

The increased sensitivity to stimulant drugs following stress exposure also has been demonstrated neurochemically through increases in dopamine activity in terminal regions implicated in drug abuse. Prior exposure to repeated food deprivation, tail pinch, foot shock, or social stress increases the dopamine response to an acute injection of cocaine or amphetamine [11,16,22,26,32–34]. Likewise, prior exposure to CUS augments the dopamine release in response to high doses of methamphetamine in the dorsal and ventral striatum [35,36]. The previous studies that exposed rats to CUS assessed dopamine activity immediately following the last stressor. It is not known whether the potentiated dopamine release in response to methamphetamine persists when measured at delayed time points, when many of the behavioral effects are reported for behavioral sensitization to stimulants. In the present study, dopamine release to an acute injection of methamphetamine was characterized immediately or within 2 weeks following the presentation of last unpredictable stressor. Based on the previous research, we hypothesized that exposure to 10 days of unpredictable stress would enhance the dopaminergic and behavioral responses to an acute injection of methamphetamine and that imposing a delay would further augment these measures.

2. Materials and methods

2.1. Animals

Sixty-two adult (PD75-120), male Sprague Dawley (Charles-River derived; Indianapolis, IN) rats were bred in the Psychology Department's animal colony at Northern Illinois University. Lights were maintained on a 12-h light:12-h dark cycle (lights on at 6 h) with temperature maintained at $22 \pm 2\,^{\circ}C$. Food and water were provided *ad libitum*. The procedures in the current studies were approved by the local Institutional Animal Care and Use Committee and followed Guide for the Care and Use of Laboratory Animals [37].

2.2. Drug injections

All rats were injected once with 7.5 mg/kg (+)-Methamphetamine HCl (6.03 mg/kg free base; Sigma Aldrich Laboratories, St. Louis, MO, USA) during testing in either the open field test or during microdialysis. Methamphetamine was dissolved in 0.9% NaCl saline and administered through an intraperitoneal (ip) injection.

2.3. Procedures

At approximately 60 days old, rats were transferred into the experimenter's laboratory colony room and handled for 5 min per day for 5 days and weighed daily (09:00) to monitor their overall health. Rats were randomly assigned either to a non-stressed control group or to a chronic unpredictable stress group (CUS). The CUS rats were further divided into rats to be tested immediately following the final stressor or those tested 1–2 weeks following the termination of the final stressor. For 10 days, rats in the CUS group received stressors applied quasi-randomly, twice a day as previously published [35,38]. The stressors included 4 h wet bedding, 16 h food and water deprivation, lights on overnight (12 h), 2 or 3 h lights off during the light cycle, 15, 20 or 50 min rotating on a shaker table, 15 or 60 min cold room (2 °C) isolated in a mouse cage, isolated in a rat cage overnight (12 h) and 60 min restraint stress in a Plexiglas restrainer (Harvard Apparatus, Hollison, MA).

2.4. Open field

A large plywood box (48 cm × 48 cm × 46 cm) painted black was used to assess locomotion. Each rat was placed into a randomly chosen corner of the open field to start and then allowed to explore the open field for a total of 120 min for 2 consecutive days. On the first day, the rat was placed into the open field for 30 min, then briefly removed for an i.p. injection of 0.9% saline and allowed to explore the open field for another 90 min. The procedures were the same on the second day with the rat receiving an i.p. injection of 7.5 mg/kg methamphetamine instead of saline. Both testing sessions were recorded using a DVD-recorder attached to an overhead camera. Distance traveled and movement speeds were measured using the Noldus EthoVision (3.0) tracking software system (Noldus Information Technology, Wageningen, Netherlands). Five samples per second were taken to track the path of the rat.

2.5. Surgery and microdialysis

Six days prior to microdialysis, a guide cannula was implanted above the dorsal striatum as previously reported [35]. For rats tested immediately following CUS exposure, the surgery was considered the stressor and no additional stressors were applied for that day. Rats were anesthetized with a combination of xylazine (6 mg/kg) and ketamine (70 mg/kg) and placed into a Kopf stereotaxic frame. A 21 gauge stainless steel guide cannula (11 mm in length, Small Parts, Inc., Miami Lakes, FL, USA) was implanted above the dorsal striatum (+1.2 mm anterior and ±3.2 mm medial to bregma) and secured by three metal screws and cranioplastic cement. A 27 gauge stainless steel obturator was inserted into the cannula until the day of dialysis. Antibiotic treatment was put on the incision site and the rat was monitored during recovery from anesthesia and weighed daily to assess health.

The day of microdialysis, the obturator was removed from the guide cannula while the rat was gently restrained with a glove. A microdialysis probe was very slowly inserted through the cannula. Microdialysis probes were constructed within our laboratory using methods described in [39]. The exposed portion of the dialysis membrane extended beyond the guide cannula into the dorsal striatum (ventral from dura −1.0 to −5.00 mm). The rat was returned to its Plexiglas cage and attached to a tether and swivel (Instech Laboratories, Inc., Plymouth Meeting, PA, USA). Dulbecco's phosphate-buffered saline medium (NaCl 138 mM, 2.1 mM KCl, 0.5 mM $MgCl_2$, 1.5 mM KH_2PO_4, 8.1 mM NaH_2PO_4, 1.2 mM $CaCl_2$, and 5 mM D-glucose, pH 7.4) was perfused at a rate of 2.0 μl/min through the microdialysis probe using a KD Scientific syringe infusion pump (Fisher Scientific, Inc., Pittsburg, PA). After a 3 h equilibration period, the following 15 min samples were collected: 3 baseline samples and 8 post methamphetamine injection (7.5 mg/kg i.p.) samples. The samples were immediately injected