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Research report

Single prolonged stress effects on sensitization to cocaine and cocaine self-administration in rats

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HIGHLIGHTS

- Posttraumatic stress disorder (PTSD) is often comorbid with substance use disorder (SUD).
- Single prolonged stress (SPS) in rodents can model comorbid PTSD and SUD.
- SPS enhances sensitization to cocaine-induced locomotor activity.
- SPS does not affect simple cocaine self-administration.
- Enhanced sensitization suggests shared neurocircuitry between PTSD and SUD.

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ABSTRACT

Posttraumatic stress disorder (PTSD) is often comorbid with substance use disorders (SUD). Single prolonged stress (SPS) is a well-validated rat model of PTSD that provides a framework to investigate drug-induced behaviors as a preclinical model of the comorbidity. We hypothesized that cocaine sensitization and self-administration would be increased following exposure to SPS. Male Sprague–Dawley rats were exposed to SPS or control treatment. After SPS, cocaine (0, 10 or 20 mg/kg, i.p.) was administered for 5 consecutive days and locomotor activity was measured. Another cohort was assessed for cocaine self-administration (0.1 or 0.32 mg/kg/i.v.) after SPS. Rats were tested for acquisition, extinction and cue-induced reinstatement behaviors. Control animals showed a dose-dependent increase in cocaine-induced locomotor activity after acute cocaine whereas SPS rats did not. Using a sub-threshold sensitization paradigm, control rats did not exhibit enhanced locomotor activity at Day 5 and therefore did not develop behavioral sensitization, as expected. However, compared to control rats on Day 5 the locomotor response to 20 mg/kg repeated cocaine was greatly enhanced in SPS-treated rats, which exhibited enhanced cocaine locomotor sensitization. The effect of SPS on locomotor activity was unique in that SPS did not modify cocaine self-administration behaviors under a simple schedule of reinforcement. These data show that SPS differentially affects cocaine-mediated behaviors causing no effect to cocaine self-administration, under a simple schedule of reinforcement, but significantly augmenting cocaine locomotor sensitization. These results suggest that SPS shares common neurocircuitry with stimulant-induced plasticity, but dissociable from that underlying psychostimulant-induced reinforcement.

Abbreviations: SUD, substance use disorder; FR, fixed ratio; Meth, methamphetamine; PTSD, posttraumatic stress disorder; SPS, single prolonged stress; NP, nose-pokes.

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1. Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that is increasingly a significant health concern and treatment management is problematic, e.g. high dropout and low success rates [1]. Poor treatment outcomes may be related to the high co-occurrence of drug use or substance use disorders (SUD) with PTSD [2,3]. Specifically, PTSD has been reported to be significantly more prevalent in cocaine-dependent individuals, with prevalence ranging from 10% to 42% [4,5], and PTSD is observed to precede cocaine abuse in 2/3 of individuals with comorbid PTSD and cocaine SUD [6]. This is particularly significant considering that SUD exacerbates PTSD symptoms and is associated with poor adherence to PTSD treatment [7]. In addition, PTSD complicates the management of SUD, resulting in poor treatment efficacy for both disorders. Furthermore, cocaine-dependent individuals with PTSD are at higher risk of having co-occurring psychiatric pathologies and poorer treatment outcomes than cocaine-dependent individuals without PTSD [8,9]. Assessing preclinical models of PTSD and SUD will lead to better understanding of comorbidity, specifically how PTSD affects the sensitizing and reinforcing effects of drugs of abuse.

Increased glutamate and dopamine release at the level of the nucleus accumbens and a host of morphological and functional changes in striatal medium spiny neurons (MSNs) are commonly associated with behavioral sensitization [10]. Drug-induced neuroplasticity is associated with increases in the reinforcing effects of drugs of abuse, increases in drug seeking behaviors, and escalation of drug intake [11–13]. In addition, acute or repeated stress has been shown to produce similar changes in the striatal neurocircuitry underlying sensitization (i.e. cross-sensitization) [14–17]. However, the effects of PTSD-like stress on this circuitry are not clear or altogether unknown.

Single prolonged stress (SPS) is a preclinical rat model associated with distinct PTSD-like characteristics [18,19]. Previous evidence from our laboratory indicates that SPS increases sensitization to methamphetamine (Meth)-induced ambulatory activity, yet attenuates sensitization to Meth-induced stereotypy [20]. This implies that SPS may induce neural adaptations to striatal dopamine release, cortical glutamatergic regulation of striatal MSNs, and/or functional changes in striatal MSNs. Moreover, our previous study provides preliminary evidence for shared neurocircuitry in PTSD and SUD. However, it is unclear whether SPS increases or decreases the reinforcing effects of drugs of abuse or whether the effects of SPS extend beyond Meth to other drugs of abuse, such as cocaine.

The goal of the present study was to determine whether SPS enhances the behavioral effects of cocaine. The effect of SPS on subthreshold sensitization to cocaine-induced locomotor activity and cocaine self-administration were examined.

2. Material and methods

All experimental procedures were approved by the Institutional Animal Care and Use Committee at Wayne State University and at the University of Michigan prior to experimentation. Wayne State University and the University of Michigan maintain campus-wide AAALAC-accredited facilities.

2.1. Animals

Adult male Sprague–Dawley rats (Charles River Laboratories, Portage, MI) were allowed to acclimate to the vivarium prior to experimentation. Rats were group housed in pairs, generally with a conspecific of the same treatment group, in standard microisolator rat polycarbonate cages with bedding. Animals were allowed food and water ad libitum in their home cages and housed on a 12 h light/dark cycle with lights on at 7 AM. Temperature and humidity were controlled in the vivarium and behavioral testing laboratories.

2.2. Drugs

(−)Cocaine hydrochloride (NIDA Drug Supply Program, Bethesda, MD) was dissolved in sterile saline (0.9% NaCl) and injected intraperitoneally (i.p.) for sensitization testing or delivered by intravenous (i.v.) catheter during self-administration procedures. Sterile saline was used as vehicle.

2.3. Single prolonged stress (SPS)

Half of the animals were exposed to the SPS procedure as previously described [20–22]. Briefly, rats were restrained for 2 h, followed immediately by a 20 min forced group swim (n = 6–8 rats per swim), allowed to recover for 15 min in a homecage, and then exposed to diethyl ether until unconscious. The remaining rats were designated as controls and were briefly handled on the day of SPS treatment. For sensitization testing, animals were left undisturbed in their home cages for 7 days prior to testing, except for weekly cage changes. For self-administration, animals were surgically implanted with femoral catheters within 8 h, but no less than 6 h, after recovery from the SPS or control treatment. After surgery, animals were left undisturbed for 7 days other than flushing catheters every other day with heparinized saline (see Section 2) and routine cage changes once per week. Surgery was conducted after SPS treatment to avoid unintended occlusions of the catheters during the SPS exposure and shortly after SPS to avoid any potential disturbances during the undisturbed period of the SPS paradigm, which has been previously reported to be necessary for the incubation of a PTSD-like phenotype [23–25].

2.4. Cocaine locomotor activity testing

One week after SPS exposure, cocaine-induced locomotor activity was assessed. We employed a modification of a sensitizing paradigm, sub-threshold sensitization, which we have shown in our lab does not produce sensitization in controls but yields sensitization in stress rats [20]. Control and SPS rats received either cocaine (10 mg/kg, n = 11 rats per group; 20 mg/kg, n = 10 rats per group) or saline (n = 10 rats per group) and were individually placed into polycarbonate testing chambers (45 cm × 26 cm × 21 cm) devoid of bedding material. Test chambers were placed in an automated monitoring system (Digiscan DMicro, Accuscan Instruments, Columbus, OH) consisting of 16 parallel infrared emitter/detector photocells mounted on a metal assembly. Locomotor activity was recorded as total photocell beam breaks (i.e. ambulation and non-ambulating movements) during the first 10 min following cocaine or saline administration. Rats were tested daily for 5 consecutive days.

2.5. Cocaine self-administration

2.5.1. Surgery

Rats scheduled for cocaine self-administration were implanted surgically using aseptic conditions with a single chronic indwelling catheter in the left femoral vein under ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) anesthesia. The analgesic carprofen (Rimadyl, 5 mg/kg, subcutaneous; s.c.) was administered immediately before and once daily for 1–2 days post-surgery. Catheters were threaded s.c. under the skin and attached to stainless steel tubing in a mesh tether button, exiting through a 1 cm incision between the scapulae. Catheters were flushed every other day with