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

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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 20mg/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 20mg/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.

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Keywords

Posttraumatic stress disorder; Single prolonged stress; Animal model; Cocaine; Sensitization; Self-administration

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 sub-threshold 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 12h light/dark cycle with lights on at 7AM. 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 2h, followed immediately by a 20min forced group swim ($n = 6 - 8$ rats per swim), allowed to recover for 15min 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 8h, but no less than 6h, 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 (10mg/kg, $n=11$ rats per group; 20mg/kg, $n=10$ rats per group) or saline ($n=10$ rats per group) and were individually placed into polycarbonate testing chambers (45cm × 26cm × 21cm) 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 10min 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 (90mg/kg, i.p.) and xylazine (10mg/kg, i.p.) anesthesia. The analgesic carprofen (Rimadyl, 5mg/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 1cm incision between the scapulae. Catheters were flushed every other day with 0.5 ml of heparinized saline (50 U/ml) in order to maintain catheter patency.

2.5.2. Apparatus—All self-administration sessions were conducted in operant conditioning chambers (30.5cm × 24cm × 21cm) placed inside sound attenuating cubicles (Med Associates Inc., St. Albans, VT). Each chamber is equipped with two nose-poke devices (ENV-114BM; Med Associates Inc.) positioned 3cm above the stainless steel grid floor and a white house light on the opposite wall. A variable rate infusion pump (PHT-107; Med Associates Inc.) delivered drug or vehicle infusions through Tygon tubing and a spring tether connected to a fluid swivel (Instech Laboratories Inc., Plymouth Meeting, PA) on a counter-balanced arm (PHM-110-SAI; Med Associates Inc.).

2.5.3. Acquisition of self-administration—Self-administration experiments were conducted within an acute exposure period following SPS (< 30 days from SPS treatment) [20,26]. Prior to daily self-administration sessions, catheters were flushed with heparinized saline and rats were tethered in the operant conditioning chambers. Sessions began with illumination of a yellow light in the active nose-poke (NP) only. Responses in the active NP produced a cocaine infusion of 0.1 ($n = 6$ rats/group) or 0.32 mg/kg/infusion ($n = 9$ /group; 100ml/kg/1–2s infusion) under a fixed ratio 1 (FR1) schedule of reinforcement. A response in the active NP coincided with illumination of the house light and extinguished the NP light for a 10s time-out during which no cues were available but NPs were recorded. Rats continued on the FR1 schedule daily for 16 consecutive sessions, each of which lasted for 60 min. Responses in the inactive NP were recorded, but had no programmed consequence. These two doses were chosen to determine if there were any dose dependent effects on self-administration. For example, previous work has demonstrated that both cocaine doses used in the present study are self-administered but 0.1mg/kg/infusion maintains greater rates of responding for drug operanda [27,28]. However, higher doses of cocaine have been shown to produce increases in cocaine self-administration and produce faster transitions to ceiling cocaine intake than lower doses [28]. PTSD produces deficits in reward function [29,30] and PTSD patients may require greater stimulation for pleasure. Therefore, we hypothesized that SPS, modeling PTSD, may produce greater maximal cocaine intake and increases the rate at which maximal intake is obtained.

2.5.4. Extinction—After 16 cocaine self-administration sessions, rats were exposed to extinction conditions for 60min per day for 5 consecutive days. During extinction sessions, rats were placed in the operant conditioning chambers, but responding on either NP had no consequence and no cues (e.g., NP light, house lights, or infusions) were available.

2.5.5. Reinstatement—After the extinction training period, a single reinstatement session was conducted, during which responding on the illuminated, active NP resulted in illumination of the house light and activation of the infusion pump; however, the cocaine solution was replaced with saline.

2.6. Statistical analysis

All statistical analyses were conducted using SPSS Statistics 17.0 (SPSS, Inc.) or Prism6 (Graphpad). Locomotor activity was analyzed using 3-way (SPS $\times$ Dose $\times$ Day) mixed-design ANOVAs followed by planned Sidak-corrected comparisons. We also assessed the % of increase in locomotor activity from Day 1 to Day 5 using 2-way (SPS $\times$ Dose) ANOVA followed by planned Sidak-corrected comparisons. Self-administration was assessed in three phases: test for acquisition (Day 16), extinction (17–21), and reinstatement (22). Acquisition responses on each type of NP (active and inactive) were examined using separate two-way (SPS $\times$ NP Type) repeated measures ANOVAs at each dose followed by Sidak-corrected post hoc tests for simple and main effects. Reinstatement phase responding was also assessed using separate two-way (SPS $\times$ NP Type) repeated measures ANOVAs. Active NPs during the extinction phase were examined using separate two-way (SPS $\times$ Extinction Day) ANOVAs for each dose. In addition, AUC analysis was conducted for the acquisition period (Days 1–15). AUC total area across this acquisition period was computed using the trapezoidal rule to approximate the curve for each individual animal using Prism 6 (Graphpad). Repeated measures ANOVAs were conducted for each dose to determine the effects of SPS $\times$ NP Type on AUC. Confidence intervals were set at 95% ($p < 0.05$). Statistics for omnibus tests are reported only for significant main effects and interactions. The data are expressed as the mean $\pm$ standard error of the mean.

3. Results

3.1. SPS dose-dependently enhanced the locomotor response to repeated cocaine

Rats were assessed for the effects of SPS on acute (Day 1; Fig. 1a) cocaine-induced locomotor activity and whether SPS would produce sensitization (Day 5; Fig. 1b) to cocaine-induced locomotor activity in a sub-threshold sensitization paradigm. 3-Way ANOVA only revealed a significant main effect of dose [$F(2, 53) = 22.2, p < 0.001$], indicating that cocaine dose-dependently increases loco-motor activity regardless of group and day, but the analysis did not reveal additional statistically significant main effects nor any significant interaction effects (statistical results not shown). Planned a priori Sidak-corrected comparisons, however, revealed that, on Day 1 non-stressed controls showed increased activity to an acute dose of cocaine at 20mg/kg ($p < 0.001$), but not 10mg/kg ($p > 0.05$), compared to saline (Fig. 1a). In addition, acute 20mg/kg produced greater activity than 10mg/kg cocaine ($p = 0.004$). Interestingly, SPS decreased the acute effects of cocaine (20 mg/kg) compared to controls also receiving 20mg/kg ($p = 0.005$). Furthermore, neither

the 10 nor 20mg/kg dose of cocaine on Day 1 produced an increase in locomotor activity compared to saline ($p > 0.05$ for both comparisons) in SPS rats. However, by Day 5 we observed an increase in cocaine-induced activity in SPS rats at the 20mg/kg dose evidenced by significantly greater activity compared to saline ($p = 0.001$) and 10mg/kg ($p = 0.050$), as well as an increase in cocaine-induced activity from Day 1 to Day 5 ($p = 0.003$; Fig. 1b), suggesting that SPS produced sensitization. We did not see any increase in cocaine-induced activity across days in SPS rats at the lower dose ($p > 0.05$). As expected using the sub-threshold sensitization paradigm, cocaine-induced activity, at either dose ($p > 0.05$ for both comparisons), did not increase across days in controls. However, as at Day 1, on Day 5 repeated cocaine at 20mg/kg still produced increased activity compared to saline ($p = 0.004$).

We additionally assessed the degree of sensitization, defined by the % increase in locomotor activity from Day 1 to Day 5, in SPS and cocaine dose groups (Fig. 1c). The ANOVA revealed a significant main effect of SPS [$F(1, 53) = 6.53, p = 0.041$] and a significant interaction of SPS and dose [$F(2, 53) = 3.25, p = 0.047$]. In addition, the main effect of dose trended toward significance [$F(2, 53) = 3.11, p = 0.053$]. Planned comparisons revealed that SPS rats that received 20mg/kg cocaine presented activity around 600% greater than their Day 1 activity. Compared to controls receiving 20mg/kg cocaine, which as expected did not show sensitization using the current sub-threshold paradigm, SPS rats had greater % increased activity, i.e. sensitization ($p = 0.035$). In addition, the 20mg/kg dose of cocaine produced sensitized activity compared to SPS rats receiving saline ($p = 0.042$), but not greater than SPS rats receiving the lower dose of cocaine ($p > 0.05$).

3.2. SPS did not affect cocaine self-administration

A separate group of rats was assessed for cocaine self-administration behavior for 0.32 mg/kg/infusion (Fig. 2a to c) or 0.1 mg/kg/infusion (Fig. 2d to f), specifically evaluating acquisition (Fig. 2a and d), extinction (Fig. 2b and e), and cue-induced reinstatement behavior (Fig. 2c and f) across 22 days. In order to complete testing within the specified experimental period, some rats may not have reached stable responding for cocaine infusions during daily 60min sessions. Stable levels of responding were defined as three consecutive sessions with less than a 20% difference and no increasing or decreasing trend in responding. Seven out of nine non-SPS and SPS rats acquired stable levels of responding for 0.32mg/kg/infusion cocaine within an average of 10.4 d (± 0.5 d) and 10.9d (± 1.2 d), respectively. The two rats in the non-SPS and SPS groups that did not acquire stable responding of 0.32 mg/kg/infusion were excluded from the analyses. Across the acquisition period (days 1–15), the number of active NP responses did not differ between non-SPS and SPS groups (Fig. S1a; $p > 0.05$ for SPS and interaction of SPS $\times$ Day). In addition, AUC analysis across the acquisition period did not reveal differences in the AUC between non-SPS and SPS groups in either active or inactive NP (Fig S1c; $p > 0.05$ for SPS and interaction of SPS $\times$ NP). On Day 16, the test for acquisition, the number of responses for cocaine infusions (0.32mg/kg/infusion) did not differ between non-SPS and SPS rats (Fig. 2a; $p > 0.05$ for SPS and interaction of SPS $\times$ NP Type). During extinction (days 17–21) when no cocaine infusions or cocaine-paired cues were available, responding rapidly decreased to less than 10 responses, and there were no statistical differences in active NP

responding during extinction between non-SPS and SPS rats (Fig. 2b; $p > 0.05$ for SPS and interaction of SPS $\times$ Extinction Day). After extinction, when the cocaine-paired cue was reintroduced but no cocaine was available (Day 22), rats readily resumed responding on the active NP, however no SPS-induced differences in reinstatement responding were found at either infusion dose (Fig. 2c; $p > 0.05$ for SPS and interaction of SPS $\times$ Nosepoke Type).

Supplementary Fig. S1 related to this article can be found in the online version at <http://dx.doi.org/10.1016/j.bbr.2015.02.027>.

It was expected that control rats responding for infusions of 0.1mg/kg/infusion cocaine would not acquire stable levels of responding within 16 days and thus no rats were excluded from the analyses. As expected, one of six non-SPS rats acquired stable levels of responding for infusions of 0.1mg/kg/infusion. Three of the six SPS rats acquired stable levels of responding within 16 days. Similar to what was observed at 0.32mg/kg/infusion, across acquisition (days 1–15) there was no effect of SPS on active NP responses for 0.1 mg/kg/infusion (Fig. S1b; $p > 0.05$ for SPS and interaction of SPS $\times$ Day). Supporting this, AUC for the acquisition period was not significantly different between non-SPS and SPS groups in either active or inactive NP (Fig. S1d; $p > 0.05$ for SPS and interaction of SPS $\times$ NP). On Day 16, there were no differences in the number of responses for infusions of 0.1mg/kg cocaine between non-SPS and SPS rats (Fig. 2d; $p > 0.05$ for SPS and interaction of SPS $\times$ Nosepoke Type). During extinction (Days 17–21), active NP responding rapidly decreased to less than five responses, and there were no statistical differences between non-SPS and SPS rats (Fig. 2e; $p > 0.05$ for SPS and interaction of SPS $\times$ Extinction Day). After extinction, when the cocaine-paired cue was reintroduced but no cocaine was available (Day 22), rats readily resumed responding on the active NP, however no SPS-induced differences in reinstatement responding were found at either infusion dose (Fig. 2f; $p > 0.05$ for SPS and interaction of SPS $\times$ Nosepoke Type).

4. Discussion

The current study sought to determine whether SPS, a previously validated rodent model of PTSD [18], would enhance cocaine sensitization and self-administration behaviors. SPS enhanced the sensitizing effects of cocaine on locomotor activity, replicating our previous findings of SPS effects on sensitization to Meth [20] and recent findings of SPS effects on sensitization to D-amphetamine [17]. Our results demonstrating behavioral sensitization to psychostimulants using a sub-threshold sensitization paradigm are in line with clinical findings of increased substance abuse and dependence in PTSD [3,8]. For example, in a 10 year follow-up to the National Comorbidity Survey, individuals with PTSD who were not initially dependent were 3.9 times more likely to be dependent on illicit drugs upon the follow-up survey [3]. Furthermore, PTSD symptom fluctuations are associated with the presence of cocaine SUD symptoms, suggesting a direct relationship between PTSD and cocaine abuse and/or dependence [31]. Cocaine-dependent individuals with PTSD report greater cocaine intake during times of negative emotions and physical discomfort [32]. Moreover, in individuals with comorbid PTSD and cocaine-dependence, PTSD symptom severity is predictive of trauma- and drug-cue elicited craving [33]. PTSD symptoms are also a predictor for relapse to drug-seeking in both trauma-exposed and PTSD-afflicted

individuals [34]. These findings suggest that PTSD may enhance craving and relapse in abstinent and possibly enhance drug intake.

We previously demonstrated that SPS enhanced Meth-induced ambulation, but reduced Meth-induced stereotypy following repeated administration [20]. In addition, a recent study found that animals with a low response to novelty had SPS-induced increases in behavioral sensitization to D-amphetamine, whereas high responders to novelty showed attenuated sensitization (i.e. desensitization) [17]. Our results agree with previous findings that stress, acute or chronic, enhances the sensitizing effects of drugs of abuse [14–16]. However this study is the first to the best of our knowledge to indicate that a single severe, multimodal stress exposure and subsequent incubation (undisturbed) period alters cocaine-induced plasticity.

An unexpected finding was that SPS blunted the acute cocaine response at 20mg/kg. This effect does not appear to have a direct effect on drug-taking behavior because acquisition of self-administration of cocaine was not affected by SPS. A few reasons could explain this effect. SPS increases freezing and startle-response behaviors [24,35] thus the blunted locomotor response may have been due to fear and defensive-related behaviors following SPS and in response to a novel environment (i.e. the locomotor monitoring chambers). Alternatively, a technical limitation of the locomotor monitoring system may have hindered our ability to detect cocaine-induced stereotypy and fine motor movements. Finally, striatal dopamine receptors are known to play an important role in the development and expression of sensitization. For example, sensitization paradigms and binge-pattern cocaine self-administration both up regulate D1 dopamine receptors in the striatum [36,37], and the expression of cocaine sensitization is known to require the synergistic activation of both D1 and D2 receptors [38]. The finding that SPS caused a blunted response to acute cocaine may suggest that SPS decreases the density or function of dopamine receptors acutely. However, repeated cocaine may have reversed this effect and led to a receptor state that caused enhanced sensitization. Alternatively, the number and function may also be altered after SPS exposure. Supporting this, recent clinical evidence indicates that PTSD increases dopamine transporter density in the striatum [39]. While the nature of the current observed effect remains to be fully clarified, it is clear that SPS modifies both acute and repeated cocaine-induced locomotor effects.

While SPS produced an enhanced sensitizing effect to a repeated cocaine administration, it did not affect cocaine self-administration. This is surprising considering the high incidence of cocaine abuse in clinical PTSD [8,40] and counter to our initial hypothesis. Yet, the lack of effect may be explained by a number of factors, three of which we describe here.

First, as previously noted, PTSD preferentially produces greater risk for substance abuse, however the rate of drug use and risk of comorbid drug dependence may be specific to certain drugs, such as nicotine, alcohol, or opiates [41,42]. While psychostimulant abuse in PTSD has been reported to be greater than the normal population [8,40], alcohol abuse and dependence in clinical PTSD is more prevalent than psychostimulant abuse and dependence [43]. The selection of depressant drugs by individuals with PTSD is supported by the self-medication hypothesis [44], which suggests that drugs may be chosen to alleviate specific

symptoms, mainly hyperactivity behavior. Therefore, the lack of change we observed in cocaine self-administration and cue-induced reinstatement of cocaine seeking behavior, which is hypothesized to model drug-dependent behaviors such as craving and relapse [45], may not generalize to other drugs, e.g. alcohol, opioids, or benzodiazepines. This needs to be tested experimentally, but one preclinical study supports this by showing that severe stress increases voluntary alcohol intake without affecting established drinking habits in the stress-enhanced fear learning rat model of PTSD [46].

Second, SPS may alter the sensitizing effects of cocaine, but not its direct reinforcing effects. Cocaine sensitization and self-administration do not necessarily share the same mechanism; although, much work agrees that the underlying neurobiology is common (see review by [10]). Behavioral sensitization is hypothesized to involve glutamatergic mechanisms [47], whereas the direct reinforcing effects modeled by self-administration procedures are or may be dopamine-specific [48]. However, the small differences in neurobiology between sensitization and self-administration are unlikely to explain the current finding.

Third, SPS may only alter other aspects of self-administration behaviors such as escalation of intake or motivation for drug, as measured by extended access and progressive ratio schedules of reinforcement, respectively. It is well known that extended access procedures produce escalation of intake [49] and that escalation is not typically observed in short access sessions, e.g. 60 min duration, but generally requires longer access sessions or periods of abstinence [50–52]. Progressive ratio schedules of reinforcement better assess motivation to work for drug [50,51,53]. The sensitizing effects of combined SPS exposure and cocaine may produce changes in the specific aspects of cocaine self-administration rather than direct reinforcing effects of cocaine. In addition, while we did not observe a change in cocaine cue-induced reinstatement, SPS may affect other aspects of drug reinstatement, such as stress- or drug prime-induced models. Additional studies of cocaine self-administration using other acquisition and reinstatement paradigms, as well as other drugs of abuse, are necessary to fully determine the effects of SPS on drug use, abuse, and dependence. The current studies suggest that under simple, short access schedules of reinforcement, SPS does not increase cocaine taking behavior and thus the general hypothesis that PTSD increases the reinforcing effects of all drugs of abuse can be rejected.

In conclusion, our findings indicate that SPS exposure enhances sensitization to cocaine, but does not affect cocaine self-administration, extinction, or cue-induced reinstatement of cocaine seeking under a simple schedule of reinforcement. Therefore, SPS may influence neurocircuitry underlying some aspect of drug-induced behaviors, e.g. sensitization. Traumatic-stress induced alterations in addiction-related neurocircuitry, in turn, likely underlie the high incidence of comorbid SUD observed in humans with PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SUD	substance use disorder
FR	fixed ratio
Meth	methamphetamine
PTSD	posttraumatic stress disorder
SPS	single prolonged stress
NP	nose-pokes

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.

Fig 1.

Locomotor activity induced by repeated cocaine is enhanced after single prolonged stress (SPS). Rats were exposed to SPS or control treatment and, 1 week later, were administered cocaine (i.p.) at 0, 5, or 10mg/kg immediately prior to daily locomotor testing (5 days) using a sub-threshold sensitization paradigm. Loco-motor activity was measured by total beam breaks for 10min following acute cocaine (a; 1 d) and repeated cocaine injections (b; 5 d). (a) Acute cocaine dose-dependently increased locomotoractivity in controls, but not SPS rats. SPS decreased acute cocaine (20mg/kg only) -induced locomotoractivity, compared to controls. (b) Repeated cocaine dose-dependently increased locomotor activity in both control and SPS groups. Furthermore, repeated cocaine (20 mg/kg only) enhanced locomotor activity in SPS, but not control, rats compared to acute cocaine. (c) Sensitization (% increase in beam breaks from Day 1 to Day 5) to 20mg/kg cocaine-induced loco-motor activity was enhanced in SPS compared to controls. Data are expressed as mean $\pm$ SEM. $n = 10-11$ rats/group; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for all comparisons.

Fig 2.

Single prolonged stress (SPS) does not alter cocaine self-administration acquisition, extinction, or cue-induced reinstatement. Rats exposed to SPS or control were previously trained (days 1–15) to self-administer cocaine at 0.32 mg/kg/i.v.-infusion (a–c) or 0.1 mg/kg/infusion (d–f) on a FR1 schedule of reinforcement. Active and inactive nose-pokes (NP) recorded across 60min daily sessions are presented. Rats maintained a previously acquired cocaine self-administration, as shown on Day 16, by increasing their responses on the active NP, however no SPS-induced differences were observed (a, d). Following the test for acquisition (Day 16), all rats underwent extinction training for 5 consecutive days (days 17–21; b, e). Rats extinguished their responses across extinction training days, but no SPS-induced differences were observed. Extinction was followed by cue-induced reinstatement (Day 22; c,f). Rats reinstated active NP responses, but no differences between control and SPS rats were observed. Data are expressed as mean±SEM. $n = 6-7$ rats/group.