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Chronic cocaine self-administration attenuates the anxiogenic-like and stress potentiating effects of the benzodiazepine inverse agonist, FG 7142

R. Parrish Waters, Ronald E. See *

Department of Neurosciences, Medical University of South Carolina, Charleston, SC 29425, USA

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ABSTRACT

Stress is a well-known risk factor in relapse to drug abuse. Several forms of stress in animals have been used with varied degrees of success to elicit reinstatement of drug-seeking after chronic drug self-administration. Here, we tested the ability of the benzodiazepine (BZ) inverse agonist, FG 7142, to elicit anxiety-like behavior and potentiate stress responses in rats as measured by standard behavioral and hormonal indices and for its ability to affect reinstatement of cocaine-seeking in rats with a prior history of cocaine self-administration. FG 7142 elicited anxiety-like behavior on the elevated plus maze (EPM) in cocaine-naïve rats, and cocaine-naïve rats injected with FG 7142 exhibited increased plasma corticosterone levels following EPM exposure. However, in animals with a history of cocaine self-administration, FG 7142 failed to affect elevated plus maze performance and did not affect plasma corticosterone response to the EPM. Furthermore, FG 7142 failed to reinstate cocaine-seeking, nor did it alter conditioned cue-induced reinstatement. These data indicate that the anxiety-related and stress potentiating qualities of BZ inverse agonism are attenuated in cocaine-experienced animals and do not lead to reinstatement of cocaine-seeking.

1. Introduction

Relapse to cocaine-seeking or cocaine-taking is the foremost obstacle in the treatment of cocaine addiction, and a major instigator of relapse in humans and animal models is exposure to a stressor (Shaham et al., 2000). Abstinent human cocaine addicts often report an increase in craving for cocaine following stressful stimuli (Sinha et al., 2006), and cocaine-seeking behavior can be elicited in animals extinguished from cocaine self-administration using anxiogenic-like stressors, such as intermittent footshock stress (Erb et al., 1996). Notably, the ability of stress to induce reinstatement does not generalize to all stressors, in that predator odor, restraint stress, and stress-predictive cues (e.g., a tone previously associated with footshock) all fail to elicit the reinstatement of drug-seeking (Shaham et al., 2000).

Although using footshock to reinstate cocaine-seeking is useful in understanding the clinical phenomenon of stressor induced relapse (Epstein et al., 2006), engaging stress-related systems by other means may offer some advantages in developing models of relapse. Of particular note are pharmacological agents that act on central neural mechanisms that mediate anxiety-like behavior and other stress-related responses and also elicit the reinstatement of extinguished drug-seeking (See and Waters, 2011). For example, central administration of corticotropin releasing factor (CRF), an anxiogenic peptide closely linked to mounting a stress response (Sutton et al., 1982), can reinstate cocaine-seeking by stimulating CRF receptors in multiple brain areas (Erb et al., 2001; Erb and Stewart, 1999; Shalev et al., 2010). Furthermore, the anxiogenic noradrenergic α-2 receptor antagonist, yohimbine, reinstates drug-seeking for methamphetamine (Shepard et al., 2004), cocaine (Feltenstein and See, 2006), alcohol (Le et al., 2005), and heroin (Banna et al., 2010). The reinstating properties of yohimbine are presumed to rely on presynaptic α-2 antagonism and subsequent increased norepinephrine release, which is associated with a stress response (Korf et al., 1973). However, some evidence suggests that yohimbine-induced reinstatement may involve additional mechanisms, including CRF release (Brown et al., 2009).

Expanding the repertoire of neuroactive pharmacological agents that can elicit the reinstatement of drug-seeking may elucidate additional mechanisms involved in relapse. Agonist action at the benzodiazepine (BZ) binding site of the $GABA_A$ receptor complex has been well characterized to decrease the magnitude of stress responses and the anxiety associated with the application of stress (Marin et al., 1997). While not a primary means of treatment in addiction, BZ agonists also provide some relief from the anxiety associated with cocaine withdrawal (Paine et al., 2002), a contributing cause of relapse in human cocaine addicts (Goeders, 2002). Furthermore, BZ agonists also have a demonstrated efficacy in reducing conditioned cue-induced reinstatement of cocaine-seeking (Goeders et al., 2009). The interactions of BZ agonists with stress responses and the reinstatement of cocaine-seeking demonstrate a potential role for BZ receptors in stress-related reinstatement of drug-seeking, and present a target to investigate the

* Corresponding author at: Department of Neurosciences, Medical University of South Carolina, 173 Ashley Avenue, BSB 416B, Charleston, SC 29425, USA. Tel.: +1 843 792 2487.
E-mail address: seere@musc.edu (R.E. See).

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interactions between a pharmacologically-induced stress response and the reinstatement of drug-seeking.

The BZ inverse agonist, FG 7142, is an established anxiogenic compound that elicits panic attacks in humans (Dorow et al., 1983) and increases anxiety-like behavior in rodents (File et al., 1985; Pellow et al., 1987). Furthermore, FG 7142 increases stress associated physiological markers, such as plasma corticosterone levels (Pellow and File, 1985) and central noradrenergic activity (Ida et al., 1991; Mason et al., 1998). Here, we assessed the anxiogenic-like and stress potentiating properties of FG 7142 in cocaine-naïve and cocaine-experienced animals using the elevated plus maze and measurement of plasma corticosterone. We also determined the ability of FG 7142 to reinstate extinguished cocaine-seeking, as well as to alter the reinstatement of cocaine-seeking in the presence of conditioned cues after repeated FG 7142 administration.

2. Methods

2.1. Subjects

Male, Sprague–Dawley rats (initial weight 275–350 g; Charles River, Wilmington, MA, USA) were individually housed in a temperature- and humidity-controlled vivarium on a 12:12 reverse light–dark cycle (lights off 6 AM–6 PM). All experimental procedures occurred during the dark cycle. Animals received water and standard rat chow (Harlan, Indianapolis, IN, USA) ad libitum for the duration of each experiment, except for the first 4 days of cocaine self-administration, during which animals were maintained on 20 g of standard rat chow per day to facilitate the acquisition of lever responding (Bongiovanni and See, 2008). Housing and care of the rats were carried out in accordance with the "Guide for the Care and Use of Laboratory Rats" (Institute of Laboratory Animal Resources on Life Sciences, National Research Council).

2.2. Surgery

Rats were anesthetized using a mixture of ketamine hydrochloride and xylazine (66 and 1.3 mg/kg, respectively, intramuscular [IM]), followed by equithesin (0.5 ml/kg with a solution of 8.0 mg/ml pentobarbital sodium, 34.0 mg/ml chloral hydrate, and 42.6 mg/ml magnesium sulfate heptahydrate dissolved in a 44% propylene glycol, 10% ethanol solution, intraperitoneal [IP]). Ketorolac (Sigma, St. Louis, MO, USA) was administered as a preoperative analgesic (2 mg/kg, IP). Chronic indwelling catheters were implanted into the right jugular vein using previously described methods (Feltenstein et al., 2007). Catheter patency was maintained by flushing with 0.1 ml of 70 U/ml heparinized saline immediately prior to self-administration sessions, and a 0.1 ml antibiotic solution of cefazolin (100 mg/ml; dissolved in saline) and 0.1 ml of 100 U/ml heparinized saline regimen following self-administration sessions. Polyethylene caps were used to cover the tips of catheters when the rats were not connected to infusion pumps. To verify catheter patency, rats occasionally received a 0.1 ml infusion of methohexital sodium (10 mg/ml; dissolved in 0.9% physiological saline), a short acting barbiturate that produces a rapid loss of muscle tone when administered intravenously.

2.3. Drugs

Cocaine hydrochloride (National Institute on Drug Abuse, Research Park Triangle, NC, USA) was dissolved in 0.9% physiological saline at 4 mg/ml. The beta-carboline, FG 7142 (N-methyl-β-carboline-3-carboxamide; Sigma, Sydney, Australia), was suspended at concentrations of 1, 5, 10, 20, and 30 mg/ml in saline (0.9% w/vol) using 3 drops of Tween 80 per 1 ml saline. This suspension, or the vehicle (saline plus Tween 80) was administered at a volume of 1 ml/kg IP immediately prior to testing. Yohimbine hydrochloride was placed into solution (1.25 mg/ml; Sigma-Aldrich, St. Louis, MO, USA) using sterile distilled water and administered IP (1 ml/kg) 30 min prior to testing.

2.4. Cocaine self-administration

Rats lever pressed for cocaine in self-administration chambers (30×20×20 cm) linked to a computerized data collection program (MED-PC, Med Associates, Inc., St. Albans, VT, USA). Each chamber was equipped with two retractable levers, with white stimulus lights above each lever, a tone generator, and a house light on the wall opposite the levers. This chamber was contained within a sound-attenuating cubicle equipped with a ventilation fan. Rats self-administered cocaine during daily 2-h sessions according to an FR-1 schedule of reinforcement. At the start of each session, the animal's catheter was connected to a liquid swivel (Instech, Plymouth Meeting, PA, USA) via polyethylene 20 tubing that was encased in steel spring leashes (Plastics One Inc., Roanoke, VA, USA). The house light signaled the initiation of the session and remained illuminated throughout the entire session. Lever presses on the active lever resulted in a 2-s activation of the infusion pump (0.2 mg/50 µl infusion; approximately 0.6 mg/kg/infusion) and a 5-s presentation of a stimulus complex, consisting of activation of the white stimulus light above the active lever and activation of the tone generator (78 dB, 4.5 kHz). After each infusion, responses on the active lever were recorded, but had no programmed consequences during a 20-s time-out period. During the sessions, responses on the inactive lever were also recorded, but had no programmed consequences. Daily cocaine self-administration continued until each rat had obtained self-administration criteria of 10 sessions with at least 10 infusions per session.

2.5. Elevated plus maze (EPM)

Elevated plus maze (EPM) testing occurred in a room dimly lit with red light (4 lumen LED bulbs×3) during the animals' dark phase. Animals with a history of cocaine self-administration as described above were tested on the first day of abstinence. A group of cocaine-naïve animals were also tested for comparison. Cocaine-naïve animals were catheterized to allow blood sampling, and transported/handled daily to match the handling history of cocaine-experienced animals. FG 7142 (10 mg/kg) or vehicle was administered via IP injection prior to placement on the EPM. We used a custom built EPM consisting of a platform constructed with opaque black plastic. The maze contained two open arms (50.80×11.11 cm) with clear plastic ledges (0.64 cm tall) on both sides and the end, and two closed arms (50.80×11.11 cm) with opaque black walls (40.64 cm tall) on both sides and the end. Animals were allowed 10 min to explore the apparatus, and the first 5 min of each trial was scored. Behavior was recorded using Ethovision 7.0 software (Noldus, Asheville, NC). We analyzed time spent in the open arms as an inverse measure of anxiety (Pellow et al., 1985). Total locomotion was estimated by counting closed arm entries to assess differences in general activity (Hogg, 1996).

2.6. Corticosterone radioimmunoassay

Blood samples (100 µl) were obtained from jugular catheters immediately prior to injection of FG 7142 or vehicle, and again 10 min later (following EPM exposure); maximal corticosterone responses to environmental stressors (e.g., restraint stress) are typically observed in this time frame (Sakakura et al., 1976). Whole blood samples were centrifuged for 20 min at 10,000 *g* and 4 °C. Plasma was stored at −80 °C until analysis for corticosterone (ng/ml) using a commercially available radioimmunoassay kit (MP Biomedical, Solon, OH) and a gamma counter.

2.7. Extinction and reinstatement

Following chronic cocaine self-administration, subjects underwent a series of daily 2-h extinction sessions, whereby responses on either the active or inactive lever were recorded, but resulted in no programmed consequences (i.e., no infusions and no conditioned stimulus presentations). Animals continued under extinction conditions for at least 7 days, and until they reached the criteria of 2 consecutive days with <15 active lever presses per session. Reinstatement trials began once an animal met the extinction criteria. Animals were run in three separate cohorts: FG 7142 low dose response testing (0, 1, 5, and 10 mg/kg), FG 7142 high dose response testing (0, 10, 20, and 30 mg/kg), and repeated vehicle and FG 7142 (10 mg/kg) followed by cue-induced reinstatement tests.

2.7.1. FG 7142 and reinstatement

This experiment examined the dose response effect of FG 7142 on the reinstatement of cocaine-seeking. Following extinction, rats underwent five reinstatement tests, with intervening extinction sessions (criteria of 2 consecutive days of <15 active lever presses/2-h session). Reinstatement tests consisted of a 2-h session in the self-administration chamber, during which lever presses were recorded, but resulted in no programmed consequences. Immediately prior to entering the chambers, the first group of rats received one of four doses of FG 7412 (0, 1, 5, 10 mg/kg) in a counterbalanced fashion. Following these trials, animals underwent reinstatement testing with yohimbine (1.25 mg/kg), injected 30 min prior to testing. Another group of rats received one of four doses of FG 7412 (0, 10, 20, 30 mg/kg) in a counterbalanced fashion. Our laboratory has previously utilized multiple counterbalanced reinstatement trials of this type (Feltenstein et al., 2009; Feltenstein and See, 2006; Reichel and See, 2010).

2.7.2. FG 7142 and cue-induced reinstatement

This experiment assessed the effect of repeated pretreatment with FG 7142 on conditioned cue-induced reinstatement. Once extinction criteria were met, animals first received a vehicle injection 2 h after each extinction session for 3 days. The following day, animals underwent a cue-induced reinstatement test, during which active lever presses resulted in the presentation of drug-associated cues (light and tone), but no cocaine infusions. The subjects then received an FG 7142 (10 mg/kg) injection 2 h after each extinction session for 3 days, followed by a second cue-induced reinstatement test.

2.8. Statistical analysis

Planned comparisons (two-tailed t-tests) were used to compare EPM performance in animals treated with vehicle or FG 7142. Pre- and post-manipulation plasma corticosterone levels were compared using repeated measures analysis of variance (ANOVA) and subsequent post hoc comparisons (Bonferroni posttest). Mixed factor ANOVA was used to compare active and inactive lever presses during self-administration and extinction. One-way ANOVA and post-hoc comparisons (Bonferroni posttest) were used to compare responding during reinstatement and extinction. The alpha was set at $p<0.05$ and all data are expressed as the mean ± S.E.M.

3. Results

3.1. Elevated plus maze

In cocaine-naïve animals, FG 7142 (10 mg/kg) produced an anxiety-like profile on the EPM (Fig. 1), with significantly less time spent in the open arms ($t_{16}=2.33$, $p=0.034$) when compared with vehicle injection. This effect was not observed in rats with prior cocaine self-administration experience as cocaine-experienced subjects treated with FG 7142 or vehicle spent an equivalent amount of time exploring the open arms of the EPM. FG 7142 did not affect total locomotor behavior in either group, as determined by closed arm entries (data not shown).

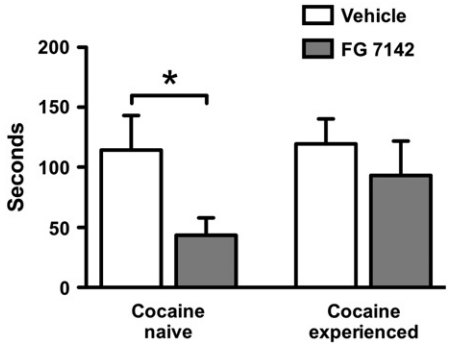

Fig. 1. Effects of acute FG 7142 on EPM performance. FG 7142 increased the anxiety-like behavior in cocaine-naïve animals (vehicle $n=8$; FG 7142 $n=10$), but not in cocaine-experienced animals (vehicle $n=10$; FG 7142 $n=11$). Cocaine-naïve animals injected with FG 7142 explored the open arms of the maze significantly less than animals injected with vehicle (*$p<0.05$), an effect that was absent in cocaine-experienced animals.

3.2. Plasma corticosterone

ANOVA revealed that FG 7142 influenced the corticosterone response of cocaine-naïve rats to EPM exposure ($F_{1,12}=17.80$, $p=0.003$). Bonferroni post-hoc tests ($p<0.05$) indicated that animals injected with FG 7142 exhibited a significant increase in plasma corticosterone following EPM exposure, and that these levels were significantly higher than animals injected with vehicle alone and exposed to the EPM (Fig. 2). In contrast, FG 7142 did not influence the corticosterone response of cocaine-experienced animals to the EPM. No animals exhibited a significant increase in corticosterone to the EPM alone (vehicle treated + EPM exposure).

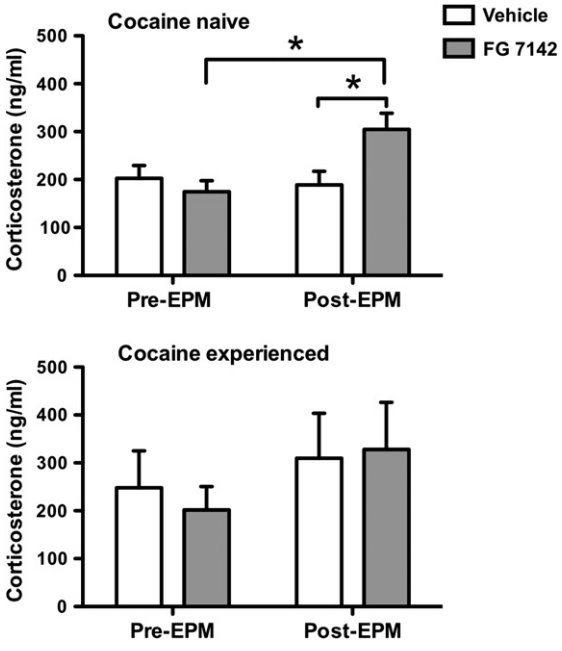

Fig. 2. Effects of acute FG 7142 and EPM exposure on plasma corticosterone levels. FG 7142 administration and EPM exposure elicited a significant increase (*$p<0.05$) in plasma corticosterone in cocaine-naïve animals (vehicle $n=8$; FG 7142 $n=6$), an effect that was not observed in cocaine-experienced animals (vehicle $n=5$; FG 7142 $n=6$).

3.3. Cocaine self-administration and extinction

All animals readily acquired and maintained cocaine self-administration criteria. Lever pressing did not significantly differ between experimental cohorts. Daily cocaine intake during self-administration was 16.6 ± 0.37 mg/kg per 2-h session (average of the last 3 days). All animals met extinction criteria following self-administration, with an average of 12.0 ± 0.74 days of extinction (summarized in Figs. 3 and 4). Inactive lever responding was uniformly low in all animals and did not differ between groups during or after self-administration.

3.4. Reinstatement of cocaine-seeking

3.4.1. FG 7142 and reinstatement

FG 7142 failed to reinstate cocaine-seeking at any dose (Fig. 3A and B); however, statistical analysis indicated a significant reduction in lever pressing at the 10 and 20 mg/kg doses ($F_{4,39} = 4.03$, $p = 0.009$; Bonferroni $p < 0.05$ compared to extinction). Following testing with FG 7142 in the first cohort (Fig. 3A), yohimbine (1.25 mg/kg) significantly reinstated cocaine-seeking in the same animals ($F_{4,123} = 5.47$, $p = 0.0004$; Bonferroni $p < 0.05$ compared to extinction).

3.4.2. FG 7142 and cue-induced reinstatement

Presentation of cocaine associated cues significantly reinstated active lever pressing ($F_{8,35} = 5.35$, $p = 0.0004$; Bonferroni $p < 0.05$ for both cue-induced reinstatement tests compared to extinction). Prior repeated treatment of animals with FG 7142 (10 mg/kg) on the 3 days preceding the second cue-induced reinstatement test did not influence lever pressing in response to cue presentation (Fig. 4).

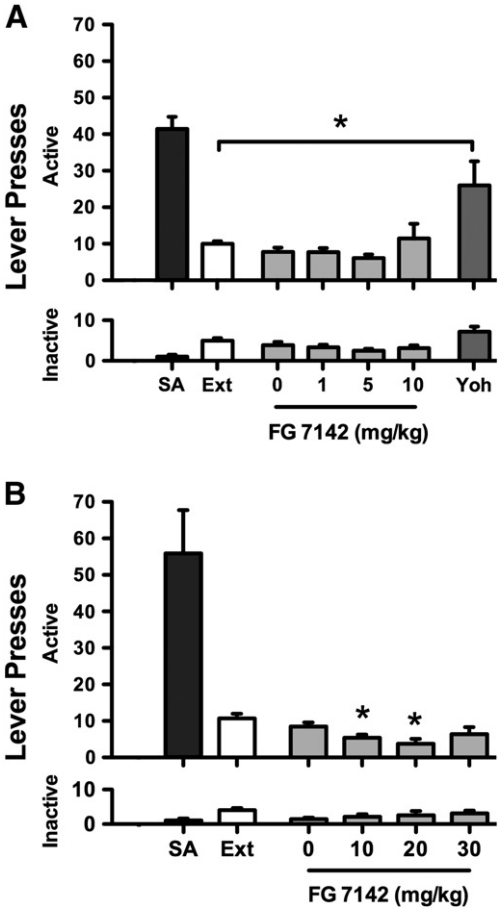

Fig. 3. Acute FG 7142 effects after chronic cocaine self-administration and extinction. FG 7142 failed to increase lever responding across a low (A; $n = 26$) or high (B; $n = 8$) dose range, with some doses of FG 7142 (B) leading to decreased responding (*$p < 0.05$). In contrast, acute yohimbine (1.25 mg/kg) significantly reinstated cocaine-seeking (*$p < 0.05$).

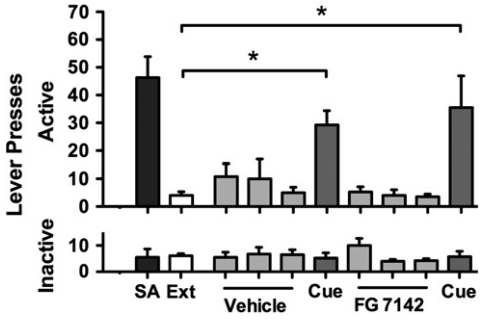

Fig. 4. The effects of pretreatment with FG 7142 on subsequent cue-induced reinstatement. Presentation of conditioned drug-paired cues reinstated cocaine-seeking (*$p < 0.05$, $n = 4$). Pretreatment with FG 7142 did not influence this behavior.

4. Discussion

The current study confirmed the anxiogenic-like and stress-potentiating qualities of FG 7142 in cocaine-naïve animals. We found these effects of FG 7142 to be attenuated in animals with a history of cocaine self-administration. Furthermore, FG 7142 failed to reinstate extinguished cocaine-seeking across a wide dose range or alter subsequent cue-induced reinstatement after repeated treatment. Our results suggest that chronic cocaine self-administration decreased the efficacy of BZ inverse agonism to induce anxiety and potentiate responses to stress. This is in contrast to other anxiogenic-like and stress-inducing environments or compounds, which show potentiation after chronic cocaine experience (Alves et al., 2008; Erb et al., 2003; Magalhaes et al., 2002; Yang et al., 1992).

Anxiety measures in rodent models (Landgraf and Wigger, 2002) allow for the assessment of an individual subject's stress coping strategy by placing them into a novel environment with stress-inducing qualities (i.e., the open arms of the EPM) and recording their behavioral reactions to this stress. The EPM is an established measure of anxiety (behavior induced by the stressful qualities of the open arms), and has been routinely used to assess the anxiogenic-like effects of pharmacological stressors, including FG 7142 (Pellow et al., 1987). In the current study, FG 7142 increased anxiety-like behavior on the EPM in cocaine-naïve animals, and elicited an increase in plasma corticosterone levels following EPM exposure, an effect not exhibited by animals treated with vehicle. These results suggest that FG 7142 elicits an anxiety-like state, and also potentiates an animal's stress response. FG 7142 failed to exhibit these effects in cocaine-experienced animals, as treatment with FG 7142 or vehicle resulted in similar levels of open arm exploration in the EPM and equivalent plasma corticosterone responses to EPM exposure. This finding was unexpected, as chronic cocaine exposure has been reported to increase the behavioral and physiological responses of rats to environmental stressors used to assess anxiety, including the forced swim test (Magalhaes et al., 2002) and the defensive withdrawal test (Yang et al., 1992), as well as to pharmacological stressors, such as CRF (Erb et al., 2003).

Cocaine-experienced animals treated with vehicle or FG 7142 exhibited non-significantly elevated plasma corticosterone levels following exposure to the EPM. This observation could reflect a slight increase in the EPM stress response in these animals as compared to cocaine-naïve animals, although unapparent in the animals' behavior on the EPM. Moderate cocaine experience, such as the regimen used herein, has previously been shown to lack an effect on anxiety-like behavior in the EPM (Mantsch et al., 2008). These minimal effects of cocaine experience on EPM performance likely result from the lower stress-inducing qualities of this test when compared to tests with more potent stress inducing qualities (e.g., forced swim test) that elicit

potentiated responses from cocaine-experienced animals (Magalhaes et al., 2002). At any rate, contrary to its effects in cocaine-naïve animals, FG 7142 did not influence anxiety-like behavior on the EPM, and failed to potentiate the stress response (i.e., further increase plasma corticosterone) of cocaine-experienced animals to the EPM. These results suggest that the anxiogenic-like and stress potentiating qualities of FG 7142 are diminished following chronic cocaine self-administration.

Reinstatement of cocaine-seeking has been reported after multiple anxiogenic-like stressors, including acute intermittent footshock stress (Erb et al., 1996; Korte and De Boer, 2003), food deprivation stress (Carroll, 1985), and yohimbine administration (Feltenstein and See, 2006; Pellow et al., 1985), although this effect does not generalize to all anxiogenic-like stressors (Shaham et al., 2000). While the anxiogenic-like and stress-inducing qualities of FG 7142 have been previously established (Evans and Lowry, 2007; File et al., 1985; Pellow and File, 1985), we found that FG 7142 failed to reinstate cocaine-seeking. In fact, two of the higher doses of FG 7142 (10 and 20 mg/kg; Fig. 3B) decreased active lever responding. While this reduction could be interpreted as freezing behavior (Conti et al., 1990) or a sedative effect (Chuck et al., 2006), this possibility is unlikely as the magnitude of change was quite small due to the very low baseline responding, and was not seen for inactive lever presses.

In contrast to FG 7142, which did not reinstate cocaine seeking, these same animals exhibited yohimbine induced reinstatement, similar to that previously reported (Anker and Carroll, 2010; Feltenstein and See, 2006). Repeated pretreatment with FG 7142 had no effect on subsequent cue-induced reinstatement, also in contrast to what has been observed with yohimbine administration (Kupferschmidt et al., 2009). Some previous studies have directly compared the behavioral and physiological effects of yohimbine and FG 7142, with some notable similarities and differences between the two drugs. Both of these compounds elicit anxiety-like behaviors, including decreased open arm time on the EPM (Atack et al., 2005; Pellow et al., 1985), decreased time engaged in social interactions (Guy and Gardner, 1985), and decreased exploration of a novel environment (Mason et al., 1998). Furthermore, both FG 7142 and yohimbine activate similar brain regions associated with stress responses as indicated by the induction of fos expression, including the bed nucleus of the stria terminalis (BNST), frontal cortex (Funk et al., 2006; Singewald et al., 2003), and basolateral amygdala (Hale et al., 2010). All of these brain structures have been implicated in the reinstatement of cocaine-seeking (Capriles et al., 2003; Erb and Stewart, 1999; McLaughlin and See, 2003), including yohimbine induced reinstatement (Funk et al., 2006; Nair et al., 2011). While similarities exist, some previously noted differences between yohimbine and FG 7142 might contribute to their divergent effects on reinstatement behavior. For example, yohimbine, but not FG 7142, increased CRF mRNA in the BNST (Funk et al., 2006), a phenomenon closely associated with stress-induced reinstatement (Erb et al., 2000). Also, while yohimbine potently and reliably elicits norepinephrine release in the frontal cortex, an effect believed to be important in the reinstatement of cocaine-seeking, reports on the ability of FG 7142 to affect this measure are inconsistent (Dazzi et al., 2002; Mason et al., 1998). The modest (compared to yohimbine) effects of FG 7142 on these specific substrates may help explain its inability to reinstate cocaine-seeking.

The failure of FG 7142 to reinstate cocaine-seeking may also relate to its unique pharmacological profile. In contrast to yohimbine, which increases norepinephrine levels through presynaptic α-2 blockade (Charney et al., 1983) and also affects other monoamines (Dzung Le et al., 2009; Millan et al., 2000), FG 7142 works via inverse agonism of the BZ receptor (Dorow et al., 1983). The lack of an FG 7142 effect on EPM behavior and the corticosterone response associated with exposure to this apparatus in cocaine-experienced animals, as well as the lack of an effect on the reinstatement of cocaine-seeking, may be due to a down-regulation of central BZ receptors associated with chronic cocaine intake, as previously reported (Goeders, 1991; McAllister et al., 1987). In spite of this finding, BZ agonists successfully decrease self-administration behavior (Goeders et al., 1989), as well as cue-induced reinstatement (Goeders et al., 2009) in cocaine-experienced animals. Thus, it appears that inverse agonist action at the BZ receptor may be selectively or preferentially altered by chronic cocaine intake.

In conclusion, we have demonstrated that the anxiogenic-like qualities of FG 7142 are attenuated in animals with a history of cocaine self-administration. Furthermore, administration of FG 7142 does not influence the corticosterone response of cocaine-experienced animals to EPM exposure. This adaptive response and the unique pharmacological properties of FG 7142 may account for the lack of an effect of FG 7142 on the reinstatement of cocaine-seeking. Future studies designed to directly assess BZ receptor levels and function in specific brain regions involved in addiction and stress responses in cocaine-naïve and cocaine-experienced animals may further reveal the role of this receptor in chronic cocaine-induced neuroplasticity and treatment response.

Acknowledgments

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