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The effects of Pavlovian cue extinction and ceftriaxone on cocaine relapse after abstinence

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Abstract

Background: Cocaine use disorder is a significant public health problem and currently no medications are FDA-approved to reduce cocaine relapse. Drug-associated cues are reported to elicit craving and cocaine-seeking in humans. Repeated, non-reinforced presentations of drug-associated cues (cue extinction) have been proposed to reduce the ability of such cues to prompt drug-seeking. In rodent models of cocaine relapse, cue extinction reduces cocaine relapse when such extinction occurs in the same context as cocaine self-administration, which is not akin to the manner in which treatment would occur in humans. Here we sought to determine whether cue extinction outside of the cocaine self-administration context would reduce relapse in the drug context. We also hypothesized that ceftriaxone, an antibiotic consistently shown to attenuate cocaine relapse in rats, would enhance the relapse-preventing effects of cue extinction.

Methods: Rats self-administered intravenous cocaine for 12 days followed by 20–21 days of abstinence. Immediately preceding the relapse test, rats either underwent 6 single daily cue extinction sessions (1hr/day) outside the self-administration context or no extinction with daily handling. Rats also received vehicle or ceftriaxone (200 mg/kg IP) on those six days.

Results: Ceftriaxone attenuated cued relapse relative to vehicle-treated rats, but there was no additive effect of cue extinction on cocaine-seeking. Cue extinction alone did not attenuate relapse.

Conclusions: Thus, in agreement with work in humans, when cue extinction is conducted outside the drug-associated context it does not reduce the risk of relapse alone. Ceftriaxone remains a strong possibility for medication to reduce cocaine relapse in humans.

Keywords

Glutamate; Relapse; Animal Model; Reinstatement

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Contributors

Authors Allison Bechard and Lori Knackstedt designed the study and wrote the manuscript. All authors reviewed and approved the final manuscript in its entirety.

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Conflict of Interest

No conflict declared.

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1. Introduction

Relapse to cocaine-seeking after periods of abstinence remains a clinical problem amongst people with cocaine use disorder. Drug-associated contexts and discrete cues maintain conditioned reinforcing effects that trigger relapse even after long periods of abstinence (e.g., Grimm et al., 2001). Pavlovian cue extinction (i.e., cue exposure therapy) involves repeated exposure to non-reinforced presentations of drug-associated cues and has been explored as a strategy to reduce the strength of cues to motivate drug-seeking. Such cue extinction reduces brain activation and self-reported cravings in cocaine-dependent individuals when the effects of extinction are tested in within-subjects designs. For example, cue extinction decreases cue-induced activation in frontostriatal brain regions relative to pre-extinction levels; however, cue-elicited cocaine craving is unaffected by cue extinction (Prisciandaro et al., 2013). Another with-in subjects' study of cocaine users found that cue extinction decreased subjective cue-induced cocaine cravings relative to pre-extinction values, with no effect on cue-induced physiological responses (Santa Ana et al., 2015).

While cue extinction is able to reduce subjective and physiological responses to drug cues, its ability to reduce relapse has not been demonstrated. For example, it has been reported that cue exposure reduces attrition and increases duration of cocaine free periods, but does not reduce likelihood of relapse (O' Brien et al., 1990). A meta-analysis of nine studies that assessed cue extinction as an intervention to prevent drug (nicotine, alcohol, opioids) relapse found no consistent evidence for its efficacy, potentially due to the therapy occurring outside the drug-taking context (Conklin and Tiffany 2002). Notably, cue extinction training occurs in the clinic, a context distinct from the drug-taking context.

Cue extinction conducted in the self-administration context reduces cued cocaine-seeking in rats (Madsen et al., 2017; Zbukvic et al., 2016). Pavlovian cue extinction conducted outside the drug-taking context reduces cocaine seeking in rats only when accompanied by systemic or intra-nucleus accumbens core (NA core) administration of the NMDA receptor partial agonist, D-cycloserine (DCS; Torregrossa et al., 2010). However, in cocaine-dependent individuals, the addition of DCS to Pavlovian cue extinction has been found to have no effect on self-reported cue-induced craving or to increase subjective and physiological responses to cocaine cues (Price et al., 2009, 2013; Prisciandaro et al., 2013; Santa Ana et al., 2015).

Here we explored the potential for another pharmacotherapeutic, ceftriaxone, to enhance the ability of Pavlovian cue extinction to attenuate relapse to cocaine-seeking. We and others have previously found that ceftriaxone attenuates cue-, and cocaine-primed relapse after instrumental extinction (Trantham-Davidson et al., 2012; Knackstedt et al., 2010a; Bechard et al., 2018). Chronic cocaine alters non-synaptic glutamate release, reuptake and signaling in the NA core, and such adaptations promote drug-seeking (see Scofield and Kalivas 2014). Following 5–7 days of ceftriaxone administration in conjunction with instrumental extinction, both the reinstatement of cocaine-seeking and the NA core glutamate efflux that accompanies reinstatement is attenuated (Knackstedt et al., 2010a; Trantham-Davidson et al., 2012). While ceftriaxone attenuates context-primed relapse after three weeks of abstinence in the absence of instrumental extinction, it is unable to normalize NA core

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glutamate efflux during such a relapse test (LaCrosse et al., 2016). Thus, ceftriaxone most effectively alters glutamate homeostasis when administered in conjunction with instrumental extinction training. As humans do not typically undergo instrumental extinction training, here we tested the effects of ceftriaxone in combination with Pavlovian cue extinction on cue-induced relapse. To further increase the translational potential of our model, we administered cue extinction training outside of the cocaine self-administration context. We hypothesized that ceftriaxone alone would attenuate cue-primed cocaine seeking after abstinence and that this effect would be enhanced by cue extinction.

2. Methods

2.1 Animals

Male Sprague-Dawley rats (n = 42; 300–350g, Charles River LLC, NC, USA) were housed in a temperature-controlled vivarium on a reverse light cycle (lights off at 7 am). All testing occurred during the dark cycle and all animal procedures were approved by the Institutional Animal Care and Use Committee of the University of Florida and performed in accordance with the Guide for the Care and Use of Laboratory Animals.

2.2 Catheter Surgery

One week after arrival in the vivarium, rats underwent surgery for implantation of an intravenous jugular catheter, as described more fully elsewhere (Bechard et al., 2018). Rats were anesthetized with a mixture of ketamine (87.5 mg/kg IP) and xylazine (5 mg/kg IP). A catheter (SILASTIC silicone tubing, ID 0.51 mm, OD 0.94 mm, Dow Corning, Midland, MI, USA) was inserted into the right jugular vein. The catheter traveled subdermally to emerge from an incision in the back. This end of the catheter was affixed to a cannula (Plastics One, Roanoke, VA) that was held in place by a rubber harness (Instech, Plymouth Meeting, PA, USA). Catheter patency was maintained with daily heparinized saline (0.1 mL of 100 units/mL, Elkins-Sinn, Cherry Hill, NJ, USA) and verified periodically using methohexital sodium (0.1 mL of 10 mg/mL, IV).

2.3 Cocaine Self-Administration

One week after surgery, rats began the self-administration of cocaine using standard operant chambers (Med Associates, St. Alban, VT; Fig. 1A). Cocaine was donated by the NIDA controlled substances program (RTI, Research Triangle, NC) and was dissolved in 0.9% physiological saline at the concentration of 4 mg/mL. Self-administration (2 hr/day) occurred on a fixed-ratio (FR)-1 schedule, wherein presses on the active lever resulted in delivery of a cocaine infusion (1 mg/kg/infusion in 0.1 mL) and the simultaneous presentation of a stimulus light over the active lever and a tone (2900 Hz, 5 sec). Presses on the inactive lever had no associated consequences. Self-administration occurred daily until rats wet the criteria of at least 9 infusions/day for 12 days. Animals not meeting this criterion were eliminated from the study (n = 2). An additional 5 rats were eliminated for losing catheter patency. One rat pressed the inactive lever more than the active lever each day of training, indicating a failure to learn the task. A total of 34 rats met cocaine self-administration criteria.

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2.4 Abstinence, Cue Extinction and Relapse Testing

Upon the conclusion of self-administration, rats began a 3-week period of abstinence during which no drug was available. During the third week of abstinence, all rats began daily treatment with either Ceftriaxone (cef) or Vehicle (veh) and either Pavlovian cue extinction training (CET) or the control condition of abstinence with daily handling (ABS) to yield four conditions: CET-cef (n = 8), CET-veh (n = 8); ABS-cef (n = 8); ABS-veh (n = 10). Cue extinction training took place in a different room than self-administration, inside modified operant boxes. The CET boxes differed from self-administration boxes on the following attributes: floor (wire mesh), walls (black), and scent (vanilla). Levers were not extended, and only the light and tone previously associated with drug infusion were presented once every 2 minutes for a total of 30 presentations. The same tone generator from the individual rats' self-administration chamber was moved to the CET chamber. After the 1 hour CET session, animals received an injection of cef (200 mg/kg IP) or veh (0.9% saline, 1 mL/kg) in accordance with our previous studies (Knackstedt et al., 2010; Bechard et al., 2018). CET/ABS and cef/veh treatment continued for 6 days. Following 6 days of CET/ABS, rats were placed back into the cocaine self-administration environment for a 2 hour instrumental extinction session where lever presses did not yield drug or cues. This was done in order to reduce the motivating value of the lever itself during the subsequent cue-primed relapse test. A post-session injection of cef/veh was given, and 24 hours later rats were assessed for cocaine-seeking in a cue-primed test of relapse, wherein presses on the previously active lever once again resulted in presentation of drug-paired cues. No cocaine was delivered during this test.

2.5 Statistical Analysis

The number of infusions, active and inactive lever presses were compared between groups later assigned to CET/ABS and cef/veh conditions using mixed factorial Repeated Measures ANOVAs with Time as a within-subject factor and Experience and Treatment as between-subject factors. The total number of infusions, inactive and active lever presses from the single extinction session and cued cocaine-seeking test were analyzed (separately) with 2-way ANOVAs with Experience and Treatment as factors in the model. Tukey's post-hoc tests controlling for multiple comparisons were used. Data were analyzed using SPSS (12.0) software.

3. Results

3.1 Self-Administration Behavior

We compared self-administration behavior (Fig. 1B) between conditions. For the number of daily infusions, there was a main effect of Time [$F_{(11,330)}$=17.7, p<0.0001] and an Experience x Time interaction [$F_{(11, 330)}$=3.1, p=0.001]. An Experience x Time interaction also was found for the number of active lever presses [$F_{(11, 330)}$ = 4.4, p<0.001], but not inactive lever presses. However, there was no difference in the total number of cocaine infusions attained over self-administration (Fig. 1C).

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3.2 Instrumental Extinction

During the single instrumental extinction session, there was no effect of Treatment or Experience, nor a Treatment x Experience interaction on active lever pressing (Fig. 2A) or inactive lever pressing (all Fig. 2B).

3.3. Cued Relapse Test

In the cue-primed relapse test, ceftriaxone attenuated cocaine-seeking, indicated by a main effect of Treatment on active lever presses [$F_{(1,30)}$=10.7, p=0.003; Fig. 2C). There was no effect of Experience (CET vs. ABS) on active lever presses, and no Treatment x Experience interaction. However, there was a main effect of Experience on inactive lever pressing [$F_{(1, 30)}$= 8.3, p=0.007; Fig. 2D]. Thus, while ceftriaxone attenuated cued cocaine-seeking, this effect was not enhanced by cue extinction training. CET experience may have promoted cocaine-seeking, as indicated by greater presses on the inactive lever during the cued relapse test.

4. Discussion

4. 1 Main Findings

Ceftriaxone attenuates cue-primed relapse to cocaine seeking after abstinence but combining cue extinction with ceftriaxone does not provide additive or synergistic attenuation. Furthermore, cue extinction alone (in the absence of ceftriaxone) did not attenuate relapse to cocaine seeking prompted by such cues. Our failure to find an effect of cue extinction training on drug-seeking induced by drug-associated cues is in agreement with the human literature that finds no effects of such extinction on craving for cocaine (Prisciandaro et al., 2013) and for alcohol, nicotine and opioids (Conklin and Tiffany 2002).

4.2 The Role of Context and Instrumental Extinction in the Ability of Cue Extinction to Reduce Relapse

Cue extinction training occurring in the drug self-administration context is capable of reducing cocaine-seeking in rodents. Following cocaine self-administration, cue exposure conducted within the drug-taking context attenuates cue-primed reinstatement of cocaine seeking in rats (Torregrossa et al., 2010; Zbukvic et al., 2016; Madsen et al., 2016). However, rats that experienced cue extinction training in a context outside of the drug-associated environment did not benefit unless they had also been treated with D-cycloserine (Torregrossa et al., 2010). We had hypothesized that based on common glutamatergic targets in the NA core, ceftriaxone would work akin to D-cycloserine to promote cue extinction in a novel context. However, we did not observe such an effect. Taken together, cue extinction conducted in a novel context is not sufficient to attenuate cue-primed reinstatement.

4.2 Ceftriaxone and Cued Relapse to Cocaine Seeking

Another important result of the present study is that following only a single instrumental extinction training session, ceftriaxone attenuated cued cocaine-seeking. This is in agreement with studies reporting beneficial effects of ceftriaxone on cue-primed reinstatement of cocaine-seeking after ≥ 9 sessions of instrumental extinction (Bechard et

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al., 2018; LaCrosse et al., 2017), and after 45 days of abstinence without extinction (Fischer et al., 2013). However, the combination of ceftriaxone and CET did not additively or synergistically reduce cued relapse. This is consistent with the work using D-cycloserine in humans, which showed that it had no effect or a worsening effect (Prisciandaro et al., 2013; Santa Ana et al., 2015) on cocaine cue reactivity.

4.3 Conclusion

In conclusion, the present data support the clinical literature in that cue extinction training conducted outside of the drug-taking environment is not itself effective at reducing drug-seeking. While the present data indicate that ceftriaxone is not a potential add-on therapy to enhance the effectiveness of cue extinction, it provides additional evidence that ceftriaxone attenuates cocaine seeking prompted by cocaine-associated cues.

Role of Finding Source

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Highlights

- Cocaine-cue extinction in a novel context does not reduce relapse
- Ceftriaxone attenuates cued cocaine seeking after abstinence
- Combined ceftriaxone and cue extinction do not synergize to reduce cued relapse

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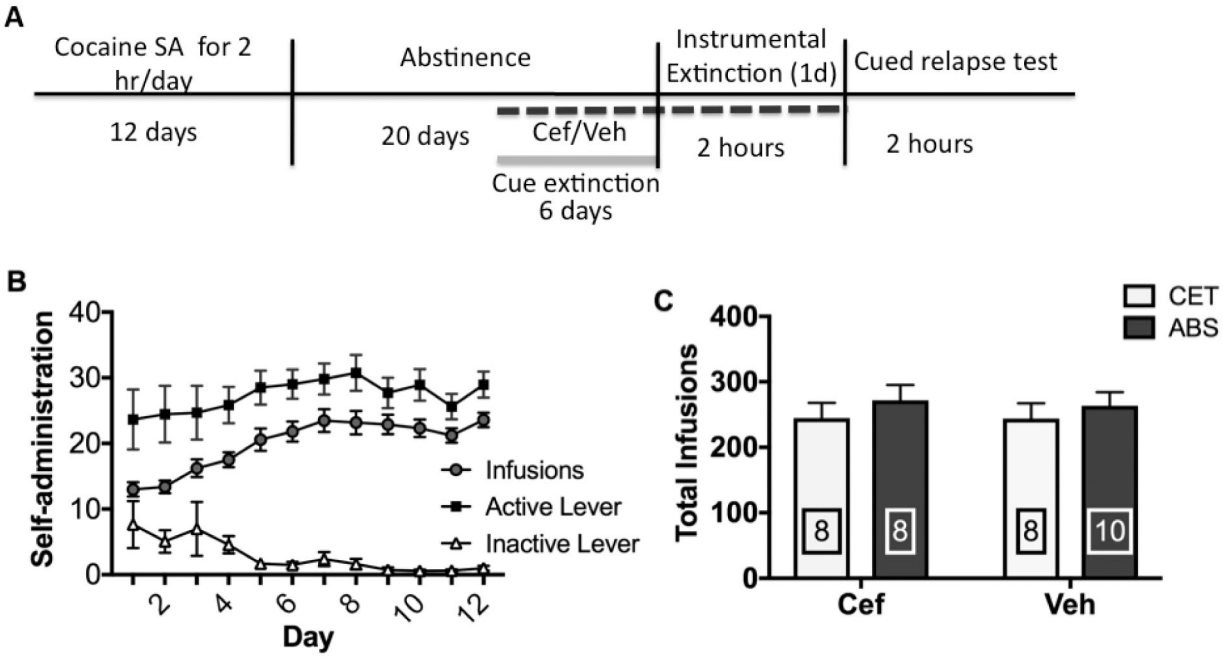

Figure 1.

A) Timeline for experimental methods. B) The number of infusions, active and inactive lever presses across 12 days of cocaine self-administration. C) The total number of cocaine infusions attained did not differ between groups later assigned to receive CET/ABS and Cef/Veh.

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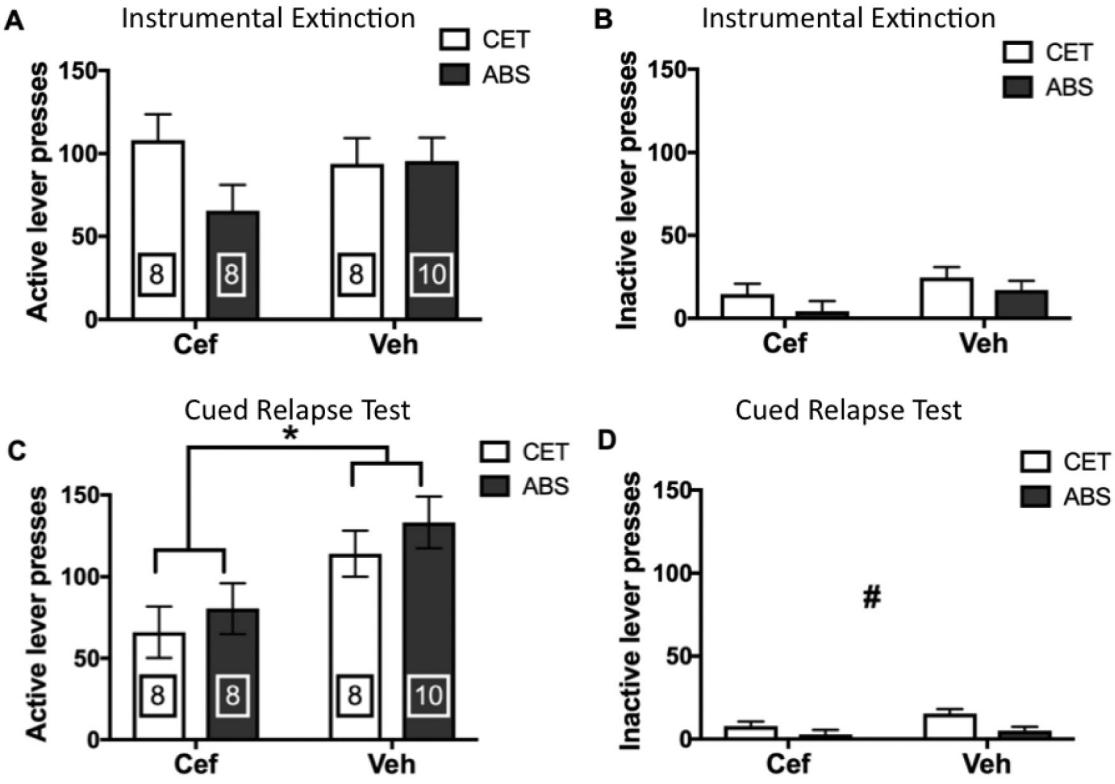

Figure 2.

The number of A) active lever and B) inactive lever presses during the extinction session were not different for rats that experienced cue extinction training (CET) and/or ceftriaxone (Cef). C) In a cued cocaine-seeking test, Cef attenuated cocaine-seeking. CET alone or in combination with CEF had no effects. D) CET rats showed increased inactive lever presses compared to ABS rats. * Cef vs Veh is $p < 0.05$; # CET vs ABS is $p < 0.05$