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Ceftriaxone attenuates cocaine relapse after abstinence through modulation of nucleus accumbens AMPA subunit expression

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Abstract
Using the extinction-reinstatement model of cocaine relapse, we and others have demonstrated that the antibiotic ceftriaxone attenuates cue- and cocaine-primed reinstatement of cocaine-seeking. Reinstatement is contingent on the release of glutamate in the nucleus accumbens core (NAc) and manipulations that reduce glutamate efflux or block post-synaptic glutamate receptors attenuate reinstatement. We have demonstrated that the mechanism of action by which ceftriaxone attenuates reinstatement involves increased NAc GLT-1 expression and a reduction in NAc glutamate efflux during reinstatement. Here we investigated the effects of ceftriaxone (100 and 200 mg/kg) on context-primed relapse following abstinence without extinction training and examined the effects of ceftriaxone on GluA1, GluA2 and GLT-1 expression. We conducted microdialysis during relapse to determine if an increase in NAc glutamate accompanies relapse after abstinence and whether ceftriaxone blunts glutamate efflux. We found that both doses of ceftriaxone attenuated relapse. While relapse was accompanied by an increase in NAc glutamate, ceftriaxone (200 mg/kg) was unable to significantly reduce NAc glutamate efflux during relapse despite its ability to upregulate GLT-1. GluA1 was reduced in the NAc by both doses of ceftriaxone while GluA2 expression was unchanged, indicating that ceftriaxone altered AMPA subunit composition following cocaine. Finally, GLT-1 was not altered in the PFC by ceftriaxone. These results indicate that it is possible to attenuate context-primed relapse to cocaine-seeking through modification of post-synaptic receptor properties without attenuating glutamate efflux during relapse. Furthermore, increasing NAc GLT-1 protein expression is not sufficient to attenuate glutamate efflux.

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1. Introduction

Cocaine addiction is a chronic relapsing disorder characterized by loss of control over drug-seeking and drug-taking, and continued drug use regardless of adverse consequences (APA, 2000). Despite almost 50 years of experimental research, effective treatments for psychostimulant addiction have not been identified. Animal models of relapse have been designed to elucidate the neurobiological processes involved in relapse behavior and to evaluate potential pharmacotherapies that may prevent or reduce the risk of relapse.

The extinction-reinstatement model is one of the most commonly used animal models in addiction research (see Epstein et al., 2006 for review). Following operant drug self-administration, the drug-seeking response is extinguished by no longer delivering drug or cues upon performance of the operant response. Over the course of days to weeks, drug-seeking behavior declines and can be reinstated by exposure to stimuli known to cause relapse in humans, including stress (Erb et al., 1996; Shaham and Stewart, 1995), discrete cues previously associated with drug delivery (Meil and See, 1996), and/or the drug itself (de Wit and Stewart, 1981). Thus, "reinstatement' is considered to be a model of relapse with adequate face and construct validity (Epstein et al., 2006). Typically, extinction training occurs in the drug-associated context (context "A"), but when it occurs in a different "B" context, the placement of animals back into context A is sufficient to "renew" lever pressing without the presentation of drug, discrete cues or stress (Crombag and Shaham, 2002).

While relapse models that utilize extinction training possess construct validity (see Epstein et al., 2006), humans do not typically experience explicit extinction training, even in clinical settings, during drug abstinence. Thus, it has been proposed that the "forced abstinence" model has greater face validity (see Reichel and Bevins, 2009 for review) in that it captures the ability of a drug-associated context to induce relapse after a period of abstinence. In this model, animals do not undergo extinction training and instead remain in the home-cage with only daily handling. "Relapse" is induced by re-exposing animals to the drug taking context (operant chamber) and execution of the previously reinforced response during this test does not result in the delivery of cues or drug (for review, Reichel and Bevins, 2009). Because extinction of the operant response does not occur in this model, the response cannot be "reinstated" and is thus referred to as "context-induced relapse after abstinence" (Knackstedt et al., 2014). A variation of this procedure is the "incubation of craving" model in which animals only experience abstinence without extinction training for 21–90 days, but the relapse test reintroduces discrete cues or drug administration (for review see Pickens et al., 2011).

The neurocircuitry underlying relapse has been found to differ substantially based on whether either extinction or abstinence procedures are employed. The stimulus used to induce reinstatement (e.g. cue vs. drug) also influences the brain regions responsible for mediating relapse. Both pharmacological and optogenetic inhibition of the nucleus accumbens core (NAc), as well as its afferents from the dorsal medial PFC (dmPFC) attenuate cue- and cocaine-primed reinstatement following extinction training (Fuchs et al., 2004; McFarland and Kalivas 2001; McLaughlin and See, 2003; Stefanik et al., 2013). While the basolateral amygdala (BLA) is not involved in cocaine-primed reinstatement (McFarland and Kalivas 2001), its pharmacological (McLaughlin and See, 2003) and optogenetic (Stefanik and Kalivas, 2013) inactivation attenuates cue-primed reinstatement after extinction. When abstinence replaces extinction training, pharmacological inhibition of the BLA and dmPFC has no effect on relapse (Fuchs et al., 2006). Conversely, inactivation of the dorsal lateral caudate putamen (dlCPu) attenuates context-primed relapse following abstinence, but has no effect on reinstatement following extinction (Fuchs et al., 2006; Mclaughlin and See, 2003). The NAc has been reported as unnecessary for abstinent-relapse to occur when animals are trained to self-administer cocaine without discrete cues (Fuchs et al., 2006; See et al., 2007). However, when cocaine self-administration is accompanied by discrete drug-associated cues (light+tone), the NAc is then demonstrated to mediate abstinent-relapse (Knackstedt et al., 2014). Additionally, the NAc has been found as essential for context-primed (ABA) renewal of drug-seeking when extinction occurs in a different context (Fuchs et al., 2008).

Glutamate dysregulation in the NAc has been identified as a primary driver of cocaine-induced reinstatement of cocaine-seeking behavior after extinction training (for review see Knackstedt and Kalivas, 2009). During cocaine-primed reinstatement following extinction training, glutamate efflux in the NAc mediates reinstatement; its release is action potential-dependent and prevented by pharmacological inactivation of the dmPFC (McFarland et al., 2003). Reduced NAc expression of the major glutamate transporter GLT-1 is present following 2–3 weeks of extinction training and is thought to contribute to the glutamate efflux observed during reinstatement (Trantham-Davidson et al., 2012). The beta-lactam antibiotic ceftriaxone increases GLT-1 expression in the NAc and attenuates cue- and cocaine-induced reinstatement (Knackstedt et al., 2010a). Ceftriaxone also prevents the increase in NAc glutamate that drives cocaine-primed reinstatement after extinction (Trantham-Davidson et al., 2012). The ability of ceftriaxone to attenuate context-primed relapse and influence GLT-1 expression and glutamate levels after abstinence have not been tested and this was the first goal of the present work.

The second, related goal of the present work was to determine the role of glutamate efflux in the NAc and post-synaptic AMPA receptor modifications in mediating context-primed relapse. Evidence for persistent glutamate adaptations following abstinence (without extinction) includes a loss of the ability to induce LTP (Knackstedt et al., 2010b) and adaptations in AMPA-receptor subunit composition (Conrad et al., 2008; Wolf and Tseng, 2012). Cocaine self-administration followed by abstinence results in the formation of GluA2-lacking, calcium-permeable AMPA receptors (CP-AMPAs) in the NAc, which underlie incubated cocaine-seeking withdrawal (Conrad et al., 2008). CP-AMPAs are found under conditions of increased total and surface GluA1 expression and unaltered GluA2 expression (Conrad et al., 2008; Wolf and Tseng, 2012). Here we examined the effects of ceftriaxone on NAc expression of GluA1 and GluA2.