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Cocaine-, caffeine-, and stress-evoked cocaine reinstatement in high vs. low impulsive rats: Treatment with allopregnanolone

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ABSTRACT

Background: Previous research indicates that individual differences in traits such as impulsivity, avidity for sweets, and novelty reactivity are predictors of several aspects of drug addiction. Specifically, rats that rank high on these behavioral measures are more likely than their low drug-seeking counterparts to exhibit several characteristics of drug-seeking behavior. In contrast, initial work suggests that the low drug-seeking animals are more reactive to negative events (e.g., punishment and anxiogenic stimuli). The goal of this study was to compare high and low impulsive rats on reinstatement of cocaine-seeking behavior elicited by cocaine (COC) and by negative stimuli such as the stress-inducing agent yohimbine (YOH) or a high dose of caffeine (CAFF). An additional goal was to determine whether treatment with allopregnanolone (ALLO) would reduce reinstatement (or relapse) of cocaine-seeking behavior under these priming conditions.
Methods: Female rats were selected as high (HiI) or low (LoI) impulsive using a delay-discounting task. After selection, they were allowed to self-administer cocaine for 12 days. Cocaine was then replaced with saline, and rats extinguished lever responding over 16 days. Subsequently, rats were pretreated with either vehicle control or ALLO, and cocaine seeking was reinstated by injections of COC, CAFF, or YOH.
Results: While there were no phenotype differences in maintenance and extinction of cocaine self-administration or reinstatement under control treatment conditions, ALLO attenuated COC- and CAFF-primed reinstatement in LoI but not HiI rats.
Conclusions: Overall, the present findings suggest that individual differences in impulsive behavior may influence efficacy of interventions aimed to reduce drug-seeking behavior.

1. Introduction

Vulnerability to drug addiction and relapse to drug seeking after termination of use is determined by both genetic and environmental factors. Studies from several laboratories have indicated that factors such as sex (Anker and Carroll, 2010b, 2011; Becker et al., 2012; Carroll and Anker, 2010), age (Spear, 2000), impulsivity (Carroll et al., 2008, 2009, 2012; Perry and Carroll, 2008), sweet preference (Dess et al., 1998, 2000, 2005; Carroll et al., 2008, 2012), novelty reactivity (Flagel et al., 2009; Kabbaj et al., 2000), prenatal stress (Frye et al., 2011), and avidity for exercise (Larson and Carroll, 2005) predict vulnerability to drug-seeking behavior, particularly with stimulant drugs. These vulnerability factors (female > male, adolescent > adult, high impulsive > low impulsive, high sweet intake > low sweet intake, high novelty reactivity > low novelty reactivity, higher avidity for exercise > lower avidity for exercise) predict elevated drug seeking throughout several phases of drug self-administration, such as initiation (Davis et al., 2008; Perry et al., 2005; Perry and Carroll, 2008; Piazza et al., 1989), escalation (Anker et al., 2009b, 2010; Perry et al., 2008), resistance to extinction after termination of drug access in rats (Belin et al., 2011; Perry et al., 2008), reinstatement of responding (relapse) after termination of drug access (Larson and Carroll, 2005; Perry et al., 2006, 2008), and they affect motivation levels under a progressive-ratio schedule (Belin et al., 2011; Carroll et al., 2002). Some of these predictors of drug self-administration, like impulsivity (Dallery and Raiff, 2007; Krishnan-Sarin et al., 2007; Yoon et al., 2007), also predict susceptibility to drug abuse in humans (Elman et al., 2001). For example higher vs. lower measures of impulsive

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behavior predict self-report of more rewarding drug effects (de Wit, 2009; Perry and Carroll, 2008).

Recent research on individual differences in drug-seeking animals indicates corresponding differences in reactivity to negative aspects related to drugs of abuse. For example, animals selected for low impulsivity (LoI vs. HiI), low saccharin intake (LoS vs. HiS), as well as adults (vs. adolescents), and males (vs. females) not only exhibit less drug seeking than their counterparts, but they also exhibit more sensitivity to punishment by histamine, greater signs of withdrawal from drugs of abuse, greater taste aversion, greater response to anxiogenic stimuli, and greater acoustic startle (Carroll et al., 2009; Carroll and Holtz, 2014; Holtz et al., 2013, 2014; Holtz and Carroll, 2014; McLaughlin et al., 2011; Radke et al., 2014, but see Radke et al., 2013), while their counterparts (HiI, HiS, adolescents, and females, respectively) have greater response to positive aspects of drugs (i.e., greater drug-seeking and drug-taking behaviors, see review by Carroll et al., 2009). This raises the question of to what extent are individual differences in drug seeking understood based on differential reactions to positive or negative aspects of drugs. Furthermore, these differing behavioral characteristics may be accompanied by underlying neurobiological characteristics (Flagel et al., 2010; Kabbaj and Akil, 2001; Regier et al., 2012) that could interact with intervention techniques, such as treatments that aim to reduce drug seeking. Therefore, differential vulnerability to drug seeking may be an important factor for customizing prevention and treatment strategies for drug abuse in humans.

To date, there have been very few preclinical animal studies that have addressed negative aspects of drugs of abuse in terms of the development and treatment of drug abuse, and there are even fewer studies in humans (Anker and Carroll, 2011; Carroll and Holtz, 2014; Holtz et al., 2013; Holtz and Carroll, 2011, 2014). In terms of prevention, it is particularly important to know how positive vs. negative aspects of drugs will affect relapse in groups that differentially administer drugs. Therefore, interventions could be matched to differences in self-administration and the specific conditions that elicit relapse. For example, studies have shown that female animals tend to show greater drug-seeking behavior than male animals (see review by Carroll et al., 2009), and female animals are more responsive to interventions that reduce drug-seeking behavior including pharmacological (Campbell et al., 2002; Carroll et al., 2001; Cosgrove and Carroll, 2004) and behavioral methods, such as access to an alternative reinforcer (Cosgrove and Carroll, 2003) or opportunity for aerobic exercise (Cosgrove et al., 2002; Zlebnik et al., 2014), available concurrently with the drug. However, in recent studies of rats selectively bred for high or low saccharin intake (HiS vs. LoS), an opposite effect occurred. The lower self-administering LoS rats reduced their rate of escalation of cocaine intake, while their higher self-administering HiS counterparts increased their cocaine escalation when treated with progesterone (Anker et al., 2012) or baclofen (Holtz and Carroll, 2011). Thus, initial evidence suggests that phenotypic differences in self-administration might determine the success of interventions aimed to reduce drug seeking.

The purpose of the present study was to further examine the reduction of reinstatement to cocaine seeking evoked by cocaine (COC), caffeine (CAFF), and yohimbine (YOH) in high (HiI) vs. low (LoI) impulsive rats treated with allopregnanolone (ALLO) or a vehicle control (VEH). Female rats were selected for HiI vs. LoI impulsivity based on their performance on a delay-discounting task that was determined by their preference for a small-immediate (HiI) vs. large-delayed food reward (LoI) as described previously (Perry et al., 2005; Perry and Carroll, 2008). Allopregnanolone has been used in previous rat studies to reduce cocaine- (Anker et al., 2009a; Anker and Carroll, 2010a) and methamphetamine- (Holtz et al., 2012) induced reinstatement of drug seeking in rats. Since ALLO, progesterone, and their precursor, pregnenolone have been show to have anxiolytic effects (Anker and Carroll, 2010a, 2011; Anker et al., 2007; Concas et al., 2000; Llaneza and Frye, 2009; Schneider and Popik, 2007), it was hypothesized that it may produce a greater reduction of stress-induced (e.g., YOH and a high dose of CAFF priming injections) responding in LoI vs. HiI animals, since LoI rats may be more sensitive to anxiogenic stimuli or other negative aspects of drugs (Holtz et al., 2013; Holtz and Carroll, 2011, 2014). Female rats were used in this study, as they show a greater difference between HiI and LoI measures of cocaine seeking than male rats (Perry et al., 2008); thus, they would provide a higher baseline of reinstatement for reduction by ALLO.

All rats were trained to self-administer iv cocaine, and their drug-seeking behavior was extinguished by substituting a saline solution. Subsequently, reinstatement responding was compared when different groups of rats were treated with ALLO or VEH before COC, CAFF, or YOH. The priming conditions were selected to simulate conditions that might elicit relapse in abstinent human drug abusers, such as COC itself, physiological stress (YOH), or a high dose of CAFF. Caffeine was included as a priming agent to serve as a model of a stimulant that is widely used in the human population and for its anxiogenic characteristics when consumed at high doses. The selected dose of CAFF (40 mg/kg) was hypothesized to have an anxiogenic effect based on evidence from previous literature. For example, an anxiogenic effect of 20 mg/kg CAFF was found in rats tested on an elevated plus maze (Gulick and Gouild, 2009; Silva and Frussa-Filho, 2000), conditioned place and taste aversions were reported in rats treated with 20 mg/kg (Steigerwald et al., 1988; Myers and Izbicki, 2006) and 32 mg/kg (Vishwanath et al., 2011) CAFF, and other measures of stress such as CAFF withdrawal have been reported (Bhorkar et al., 2014). Based on Perry et al. (2008) it was hypothesized that HiI rats would reinstate responding on the drug lever more than LoI rats to a positive priming injection (COC), and LoI would exceed HiI rats on reinstatement to anxiogenic stimuli (YOH and a high dose of CAFF).

2. Methods

2.1. Subjects

Adult female Wistar rats (total $n = 67$) were used for this experiment (see Table 1). Estrous cycle was not monitored to prevent disruption of cocaine-maintained behavior by repeated vaginal lavage (Walker et al., 2002); therefore, results can be generalized across all phases of the estrous cycle. After a minimum of 3 days of acclimation following arrival to the laboratory, rats were housed individually in plastic holding cages and moved daily into experimental chambers for delay-discounting testing. During the self-administration period following completion of

Table 1
Reinstatement groups and order of priming events.

Priming condition	*N*		Reinstatement priming sequence			
Cocaine (COC)	24	Pretreatment	VEH	VEH	VEH	ALLO
		Prime	SAL	COC	SAL	COC
Caffeine (CAFF)	24	Pretreatment	VEH	VEH	VEH	ALLO
		Prime	SAL	CAFF	SAL	CAFF
Yohimbine (YOH)	19	Pretreatment	VEH	VEH	VEH	ALLO
		Prime	SAL	YOH	SAL	YOH