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Cocaine self-administration and reinstatement in female rats selectively bred for high and low voluntary running

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ABSTRACT

Background: Previous research has found that rats behaviorally screened for high (vs. low) wheel running were more vulnerable to cocaine abuse. To assess the extent to which a genetic component is involved in this drug-abuse vulnerability, rats selectively bred for high or low voluntary running (HVR or LVR, respectively) were examined for differences in cocaine seeking in the present study.
Methods: Female rats were trained to lever press for food and then were assessed for differences in acquisition of cocaine (0.4 mg/kg; i.v.) self-administration across 10 sessions. Once acquired, rats self-administered cocaine for a 14-day maintenance phase, followed by a 14-day extinction phase when cocaine was no longer available. Subsequently, reinstatement of cocaine seeking was examined with priming injections of cocaine (5, 10 & 15 mg/kg), caffeine (30 mg/kg), yohimbine (2.5 mg/kg) and cocaine-paired cues.
Results: A greater percentage of LVR rats met the acquisition criteria for cocaine self-administration and in fewer sessions than HVR rats. No differences in responding for cocaine were observed between phenotypes during maintenance. However, during extinction LVR rats initially responded at higher rates and persisted in cocaine seeking for a greater number of sessions. No phenotype differences were observed following drug and cue-primed reinstatement of cocaine seeking.
Conclusions: In general, LVR rats were more sensitive to the reinforcing effects of cocaine than HVR rats during periods of transition into and out of cocaine self-administration. Thus, LVR rats sometimes showed a greater vulnerability cocaine seeking than HVR rats.

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1. Introduction

Recent evidence suggests that exercise is an effective treatment for drug abuse (see reviews by Bardo and Compton, 2015; Zhou et al., 2016). One potential explanation for this interrelationship is that exercise serves as a competing reinforcer for drug use. In both humans and animals, exercise is a reinforcing activity (e.g., Iverson, 1993; Raichlen et al., 2012; Ussher et al., 2012) that stimulates the same mesolimbic reward pathway as drugs of abuse (e.g., Fienberg et al., 1998; Raichlen et al., 2012). The strong interrelationship, however, is presumably bidirectional and suggests that greater reinforcing efficacy of exercise in certain individuals may indicate a vulnerability to drug abuse.

Larson and Carroll (2005) conducted the initial work on how the proclivity for exercise indicates a potential vulnerability to drug abuse. In this study, they screened (not selectively bred) wild-type rats into high and low wheel-running (HiR and LoR, respectively) groups using a median split, and then assessed cocaine seeking and the motoric effects of cocaine. Results indicated HiR rats self-administered more cocaine and showed more cocaine-primed reinstatement of drug seeking than LoR rats. However, when cocaine-induced locomotor activity was examined, LoR rats showed a relatively greater sensitivity to cocaine's motoric effects than HiR rats. These inconsistent results may have been a byproduct of prescreening rats into the high and low wheel running groups. One issue is that rats screened into the high wheel running group may have co-selected for rats that also engaged more in other rein-

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forcing activities, such as cocaine seeking. Another issue is that allowing rats to run prior to testing may have resulted in neurobiological changes that dampened the motoric effects of cocaine (see Greenwood et al., 2011; Werme et al., 2000). To address the extent to which these drug effects are genetically mediated, researchers have turned to naïve rats selectively bred for high and low running.

Roberts et al., (2012, 2013, 2014) recently developed rat strains that are selectively bred for high and low voluntary running (HVR and LVR, respectively), which is a heritable trait in both rodents (Roberts et al., 2012) and humans (e.g., De Moor et al., 2010). Brown et al. (2015) conducted the first investigation that used naïve HVR and LVR rat strains to determine if the motoric effects of cocaine in Larson and Carroll (2005) were genetically mediated. In this study, they found that LVR rats showed relatively greater cocaine-induced locomotor activity compared to HVR rats (see also Rhodes et al., 2001). Although LVRs were more sensitive than HVRs to the locomotor stimulating effects of cocaine, such motoric effects are not a reliable predictor of cocaine self-administration (Mitchell et al., 2005). Thus, it is difficult to predict how HVR and LVR rats will differ in cocaine self-administration. However, if these findings parallel Larson and Carroll (2005), who found HiR rats were more vulnerable to heightened levels of cocaine self-administration, one would predict that HVRs would show greater cocaine seeking than LVRs.

The present study examined HVRs and LVRs across all phases of the drug self-administration process. Rats were assessed in the acquisition, maintenance, extinction and reinstatement phases of cocaine seeking. Following completion of the study, expression of the HVR and LVR phenotype was assessed by allowing access to a running wheel. It was hypothesized based on the findings of Brown et al. (2015) and Larson and Carroll (2005) that HVR rats would display a genetically-mediated vulnerability to cocaine self-administration during maintenance and cocaine-primed reinstatement compared to LVR rats.

2. Materials and methods

2.1. Animals

Outbred female Wistar rat (generations 12–14) strains selected for high (n = 22) or low (n = 32) voluntary running were bred at the University of Missouri (Columbus, MO) and were tested at the University of Minnesota beginning on postnatal day (PND) 50. All rats were naïve and were not assessed for voluntary running prior to the study. Briefly, the HVR and LVR lines were bred using rats that were selected for high (e.g., >30 km/day) and low (e.g., <10 km/day), respectively, voluntary treadmill running from PND 28–34 (see Roberts et al., 2012 for additional breeding details). Female rats were used as they were used in Larson and Carroll (2005) to examine wheel running as a vulnerability factor for cocaine abuse. Additionally, females are more active in running wheels (e.g., Krasnoff and Weston, 1976) and are more vulnerable to developing cocaine-seeking behavior (see a review by Anker and Carroll, 2010b). Estrous cycle was not sampled since the primary interest of this study was to characterize HVR and LVR female rats across all reproductive phases. Rats were initially housed in rooms maintained at 24 °C (40–50% humidity) under a 12/12-h light/dark cycle (lights on at 0600) in polycarbonate cages with free access to water. At the beginning of the study, rats were food restricted to 16 g of chow per day (Harlan Teklad 2018, Madison, WI) to maintain 85% of their free-feeding weight and facilitate drug taking (Carroll et al., 1979; Lynch and Carroll, 1999). During cocaine self-administration, rats were housed in the operant conditioning chamber. The experimental protocol conformed to the Guide for the Care and Use of Animals (National Research Council, 2011) and was approved by the University of Minnesota Institutional Animal Care and Use Committee.

2.2. Operant conditioning chambers

Experimental operant conditioning chambers were custom-built and octagonal, with alternating aluminum and clear plastic panels. For the lever training with food pellets (see below), chambers were equipped with a 45-mg pellet dispenser, two response levers with stimulus lights directly above, and a ceiling light for general illumination. For the cocaine self-administration procedure, chamber levers and lights were arranged identically to Larson and Carroll (2005), and the chamber was equipped with a syringe pump to deliver response-contingent cocaine infusions based on the weight of the rat (1s/100 g) at a rate of 0.025 ml/s. Rat weights were updated weekly.

2.3. Drugs

(−)-Cocaine HCl (National Institute of Drug Abuse, Research Triangle Institute, Research Triangle Park, NC) was dissolved in a mixture of saline and heparin (5 USP/mL) at a concentration of 1.6 mg/ml. Cocaine was delivered at a unit dose of 0.4 mg/kg, which produces reliable self-administration in rats and is the same dose used by Larson and Carroll (2005).

2.4. Procedure

2.4.1. Jugular catheterization surgery. Rats were anesthetized with ketamine (60 mg/kg, intraperitoneally [*ip*]) and xylazine (10 mg/kg, *ip*) and then were given atropine (0.15 ml, subcutaneously [*sc*]) to facilitate respiration. Subsequently, an indwelling polyurethane catheter was inserted into the right jugular vein and sutured in place with silk thread (4-0). The distal end was tunneled subcutaneously to the mid-scapulae area where it exited and attached to a harness and tether system previous described (see Anker et al., 2007). Following recovery, rats were treated with buprenorphine (0.05 mg/kg, *sc*) twice daily for 72 h. An additional analgesic, ibuprofen (~50 mg/kg, PO), was provided in the drinking water. During the 3 recovery days, catheters were flushed daily with an antibiotic (enfloxacin; 10 mg/kg) and heparinized saline (10 IU/kg). To maintain patency thereafter, catheters were flushed daily with heparinzed saline, and patency was verified weekly with a 0.1 ml flush of ketamine (60 mg/ml) and midazolam (3 mg/ml) in saline (KMS). If a loss of righting reflex did not occur within 10 s of the KMS flush, a second catheter was implanted in the left jugular vein using the aforementioned methods.

2.4.2. Acquisition of IV cocaine self-administration. Rats were trained to respond for sucrose pellets (BioServ #F0021, Frenchtown, NJ) on a fixed-ratio 1 schedule of reinforcement until more than 30 reinforcers were earned in 3 consecutive 45-min training sessions. Once lever trained, rats underwent jugular catheterization surgery and commenced housing in the cocaine self-administration chambers at the start of the 3-day recovery period. After recovery, HVR (n = 22) and LVR (n = 31) rats were allowed to self-administer cocaine (0.4 mg/kg, *iv*) during daily 6-h sessions (7 days/week). The start of the self-administration session (0900 h) was signaled by the illumination of the overhead light. During the session, cocaine was infused following a response on left (i.e., "infusion") lever. During the cocaine infusion (1s/100 g), the stimulus light above the left lever was illuminated, and additional responses on this lever during the infusion were recorded but produced no consequence. A response on the right (i.e., "activity") lever illuminated the lights above that lever for the same duration as the infusion lever but produced no other consequence.