Available online at www.sciencedirect.com
SCIENCE DIRECT
Pharmacology, Biochemistry and Behavior 82 (2005) 590 – 600
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Wheel running as a predictor of cocaine self-administration and reinstatement in female rats

Erin B. Larson [a,b,*], Marilyn E. Carroll [b,1]

[a] Graduate Program in Neuroscience, University of Minnesota, MMC 392, Minneapolis, MN 55455, United States
[b] Department of Psychiatry, University of Minnesota, MMC 392, Minneapolis, MN 55455, United States

Received 9 June 2005; received in revised form 11 October 2005; accepted 25 October 2005

Abstract

Avidity for behaviors mediated by nondrug rewards, such as novelty seeking or intake of sweets or fats, is predictive of enhanced vulnerability to the locomotor-activating and rewarding effects of drugs of abuse. The purpose of the present study was to determine whether avidity for wheel running was predictive of subsequent cocaine-induced locomotor activity, cocaine self-administration, and cocaine-seeking behavior in rats. Rats with high (HiR) and low (LoR) levels of wheel running were selected from an outbred sample of Wistar rats. These rats were first tested for their locomotor response to an acute injection of cocaine (10 mg/kg, i.p.). Subsequently, a multi-phase self-administration procedure was used to examine the effect of wheel running on the maintenance, extinction, and cocaine-induced reinstatement of cocaine-seeking behavior in HiR and LoR rats. The results indicate no significant differences between HiR and LoR rats in the cocaine-induced stimulation of locomotor activity. During maintenance, HiR rats self-administered more cocaine than LoR rats. While there were no group differences in saline self-administration behavior during extinction, HiR rats showed higher cocaine-induced reinstatement than LoR rats. Rats that were previously high responders to novelty (day 1 in locomotor track) also showed significantly higher reinstatement than low novelty responders. These results suggest that a propensity for wheel running is associated with increased vulnerability for cocaine self-administration and reinstatement and that HiR rats are more motivated than LoR rats to seek cocaine.

Keywords: Wheel running; Cocaine; Locomotor; Self-administration; Reinstatement; Relapse; Drug-seeking; Female

1. Introduction

There is evidence that individual differences in drug abuse may reflect individual differences in endogenous characteristics, such as preference for sweets, activity, or novelty-seeking behavior. That is, individuals that strongly express these characteristics are more likely to abuse drugs than those that exhibit low occurrence of these traits (Carroll et al., 2001). In rats, high and low responders (e.g., rats that have high or low expression of a particular trait) can be selected from a population of outbred rats, and these animals can then be assessed on various aspects of drug-mediated behavior. The phenotype of interest can also be exaggerated by selective breeding (Dess et al., 1998). Studies using these methods show that high responders for palatable tastes (Gosnell, 2000; Gosnell and Krahn, 1992; Gosnell et al., 1995; Kampov-Polevoy et al., 1995; Dess et al., 1998; Carroll et al., 2002), novelty-seeking or novelty-induced locomotor activity (Piazza et al., 1989, 1990, 2000; Pierre and Vezina, 1997; Klebaur and Bardo, 1999; Sell et al., 2005), impulsivity (Poulos et al., 1995; Perry et al., 2005), and stress reactivity (Piazza et al., 1991; Piazza and Le Moal, 1996, 1998; Homberg et al., 2002) are more sensitive to the locomotor-activating effects of drugs of abuse, and they are more likely to self-administer drugs compared to their low-responding counterparts.

While increased vulnerability for drug-mediated behavior has been demonstrated in high responders for palatable food, novelty, impulsivity, and stress, the relative vulnerability for drug abuse has not been investigated in rats that are high and low responders for wheel running. Wheel running is a nondrug, noningestive behavior that is actively engaged in by rats, and it

* Corresponding author. Tel.: +1 612 624 4406; fax: +1 612 624 8935.
E-mail address: larso323@umn.edu (E.B. Larson).
[1] Tel.: +1 612 686 6289; fax: +1 612 6248935.

0091-3057/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2005.10.015

has reinforcing effects similar to drugs as measured using operant conditioning paradigms. Although it is unknown if there is a "natural" equivalent of wheel running, there is little doubt that it is a particularly rewarding and highly motivated behavior in rats (Sherwin, 1998). For example, rats will lever press for access to running wheels (Iversen, 1993), they show conditioned place preferences for environments associated with the aftereffects of wheel running (Lett et al., 2000), and they escalate their wheel running when given unlimited access to the wheels (Lattanzio and Eikelboom, 2003). Notably, wheel running displays several features that are similar to drug addiction, and these behaviors may have common mechanistic underpinnings. For example, both wheel running and drug self-administration are modified in the same way by the same factors; that is, feeding conditions (Finger, 1951; Carroll, 1985), access duration (Lattanzio and Eikelboom, 2003; Ahmed and Koob, 1998; Ahmed et al., 2000), sex (Hitchcock, 1925; Krasnoff and Weston, 1976; Jones et al., 1990; Lynch and Carroll, 1999; Carroll et al., 2002), and hormonal status (Rodier, 1971; Lynch et al., 2001).

The association between wheel running and the subsequent vulnerability to the reinforcing effects of drugs has been examined in only a few studies. In these, rats with or without wheel access were compared, and it was demonstrated that wheel running experience produced cross-tolerance to the rewarding effects of morphine (Lett et al., 2002). When access was given during ethanol withdrawal, it potentiated subsequent ethanol intake (Werme et al., 2002). However, it is unclear from these studies how individual differences in avidity for wheel running may have influenced subsequent drug-mediated responding. In order to address this issue, in the present study, we compared several measures of cocaine-mediated responding in outbred rats screened for either high (HiR) or low (LoR) voluntary wheel running.

One objective of the present study was to determine whether individual differences in voluntary wheel running predicted the subsequent sensitivity to the locomotor-activating effects of cocaine. Based on previous research with high and low responders for novelty (e.g., Piazza et al., 1989; Sell et al., 2005) or sugar intake (Sills and Vaccarino, 1994), we hypothesized that HiR rats would show greater locomotor activity in response to an acute injection of cocaine compared to LoR rats. A second objective of the present study was to compare HiR and LoR rats on their cocaine self-administration behavior during maintenance, and we predicted that HiR rats would self-administer more cocaine than LoR rats. Currently, the majority of research that has examined the role of individual differences on the vulnerability for drug abuse has focused on self-administration (e.g., during the acquisition phase). However, there is little information about how individual differences can affect drug-seeking behavior during abstinence (Sutton et al., 2000). Therefore, a final aim of the present study was to compare HiR and LoR rats on their cocaine-seeking behavior during extinction and reinstatement, in order to determine whether HiR rats are more motivated than LoR rats to seek cocaine under extended abstinence conditions.

2. Methods

2.1. Animals

Fourteen sexually mature ($\geq$90 days) female Wistar rats (Harlan Sprague Dawley, Madison, WI) weighing 250–340 g were used in this study. Females were used as they are more active in running wheels than males (Hitchcock, 1925; Krasnoff and Weston, 1976; Jones et al., 1990), and HiR/LoR differences were more likely to be detected. Also, there has been little work that has examined factors that predict individual differences mediating drug abuse in females (Klebaur et al., 2001; Sell et al., 2005). While wheel running has been shown to fluctuate across the estrous cycle (Steiner et al., 1982; Kent et al., 1991; Eckel et al., 2000) and can be modulated by gonadal hormones (Rodier, 1971; Morgan and Pfaff, 2002), it was not an aim of the study to examine hormonal regulation of wheel running and its relation to cocaine self-administration and reinstatement. Thus, estrous cycles were allowed to vary randomly and they were not monitored or analyzed.

Rats were acclimated to the lab for at least 3 days prior to surgery, and after surgery they were housed in their experimental chambers for the duration of the experiment. Rats had unlimited access to water and were fed ground Purina Laboratory Chow (Purina Mills, Minneapolis, MN). Food and water were replenished daily starting at 0800 h and intakes were measured and recorded at this time. Rat body weights were measured weekly. Food was available ad libitum *until surgery*. After surgery, it was reduced to 16 g/day and it remained at that amount for the rest of the experiment. We chose to slightly food restrict the rats during self-administration to accelerate training and to control for potential differences in food intake between groups. Using this procedure, food and water intake, as well as rat weights, did not differ significantly during the self-administration, extinction, and reinstatement portions of the experiment (data not shown). Throughout the experiment, all rooms were on a 12/12 light/dark cycle (lights on at 0600 h), and the laboratory was kept at constant temperature (24 °C) and humidity levels. Experimental procedures were approved by the University of Minnesota Institutional Care and Use Committee (IACUC) under protocol number 0112A13581, and laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). Principles of Laboratory Animal Care (National Research Council, 2003) were followed.

2.2. Apparatus

2.2.1. Assessment of locomotor activity

Custom-made circular stainless steel locomotor tracks were used to measure novelty-induced locomotor activity (day 1), baseline locomotor activity (day 2), and locomotor activity after acute exposure to either saline (day 31) or cocaine (day 32). Tracks had inner and outer diameters of 46 and 71 cm, respectively, and the walls were 25 cm high. Tracks were covered with a Plexiglas sheet during testing. Four infrared sensors (SE612CV, Banner Engineering Corp., Minneapolis,

MN) were mounted 5 cm above the floor of the track on the outer wall at 0°, 90°, 180°, and 270°. Two successive sensor interruptions were measured as one activity count, and counts were totaled and recorded in 5-min increments. Sensors were connected to a VersaMax programmable logic controller (IC200UDR001, GE Fanuc Automation, Charlottesville, VA), and the data were recorded using IBM-compatible computers and VersaPro software (GE Fanuc Automation, Charlottesville, VA).

2.2.2. Wheel running and i.v. cocaine self-administration

Experimental chambers consisted of an octagonal operant chamber enclosed within a sound-attenuating wooden box that was equipped with a fan for white noise and ventilation. The eight walls alternated with stainless steel or plexiglas. The interior of the operant chambers contained two response levers (MedAssociates, St. Albans, VT) mounted on two of the stainless steel panels. Stimulus lights (4.76 W) were located above each lever and they were illuminated for 20-s after each lever press. Chambers also contained a ceiling house light (4.76 W), a food hopper, and a panel for the water bottle. Each operant chamber had a guillotine-style door that, when opened, allowed access to a 35.6-cm diameter external running wheel (MedAssociates, St. Albans, VT) that was elevated 7 cm above the cage floor. Brake resistance on the wheel was set at 8. Four sensors were located along the wheel at 0°, 90°, 180°, and 270°, and every four sensor breaks were counted as one wheel revolution. An IBM-compatible computer with Med-PC interface (Med Associates, St. Albans, VT) was used for programming and data collection.

2.3. Drugs

Cocaine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC) and was dissolved in a 0.9% NaCl solution. Heparin (1 ml/200 ml saline) was added to cocaine and saline solutions in order to reduce blood clotting and to maximize the duration of catheter patency. Cocaine solutions were kept refrigerated, but they were added to the 500-ml reservoirs at room temperature. Rats received cocaine (0.4 mg/kg/inf) at a rate of 0.025 ml/s and a duration of 1 s/100 g of body weight.

2.4. Procedure

2.4.1. Assessment of locomotor response to novelty and baseline locomotor activity

Fig. 1 summarizes the sequence and timing of the experimental procedures. Prior to running wheel access, rats were tested in the circular track for 45 min on 2 consecutive days. Each individual rat was tested at the same time each day, and all rats were tested during the light portion of the light/dark cycle (between 0900 and 1400 h). Since locomotor activity was significantly lower on day 2 than on day 1 of testing (see Results), the locomotor data were analyzed by day. Data from day 1 were considered to reflect the locomotor response to novelty, whereas day 2 data were considered to reflect baseline activity levels. We assessed both the locomotor response to novelty (day 1) and baseline locomotor activity (day 2) prior to wheel running access to ensure HiR rats had more activity in the running wheels because they had more avidity for this behavior than LoR rats, and not because they were more responsive to novel stimuli or were inherently more active. We also wanted to determine whether HiR and LoR group differences were specifically due to wheel running, or if the groups also had more generic activity differences.

2.4.2. Wheel running and locomotor response to cocaine

Following initial locomotor testing, each rat was allowed access to a running wheel for 21 days, for 6 h/day beginning at 0900 h. Wheel access was then discontinued and the door to the running wheel remained closed for the remainder of the experiment. A median split was used to divide rats into HiR and LoR groups based on their average wheel running across the 21-day access period. In order to assess cocaine-induced locomotor activity in HiR and LoR groups, rats were retested on the circular track for 2 consecutive days 7 days after

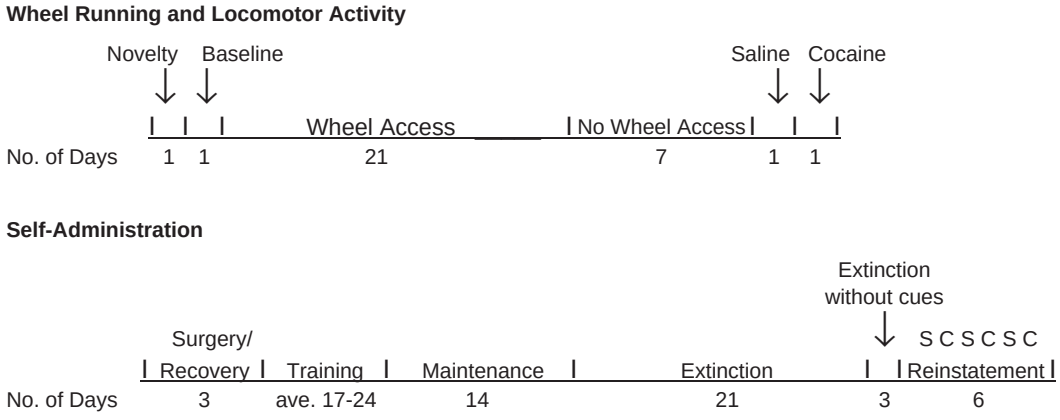

Fig. 1. Outlines of the experimental procedures are shown for the wheel running and locomotor activity (top) and self-administration (bottom) portions of the experiment. The length of each phase is represented underneath. SCSCSC indicates the priming injection order during reinstatement testing (S=saline injection, C=cocaine injection, 10 mg/kg, i.p.).

discontinuation of wheel access (experimental days 31 and 32). On the first day (day 31), rats received an intraperitoneal (i.p.) injection of saline just prior to being placed on the track, and on the second day (day 32) they were injected with 10 mg/kg cocaine (i.p.) prior to track placement. Animals were tested at the same time each day and at the same time that they were tested on days 1 and 2.

2.4.3. Surgery

After the second round of locomotor testing, rats were implanted with jugular catheters for intravenous (i.v.) cocaine self-administration. Each rat was anesthetized with ketamine (90 mg/kg) and nembutal (10 mg/kg), and was supplemented with atropine (0.15 cc). Each rat was then implanted with a chronic, indwelling jugular catheter. The silastic catheter was secured to the vein with silk sutures (Genzyme, Fall River, MA), and the free end was led subcutaneously around the back and exited midscapular region. The free end of the catheter tube was then attached to a cannula connector (C3236; Plastics One, Roanoke, VA) imbedded in a covance infusion harness (Instech Laboratories, Plymouth Meeting, PA) that connected to the infusion system. This system contained an external infusion pump (RHSYOCKC, Fluid Metering, Oyster Bay, NY) that was connected on one end to a 500-ml reservoir containing cocaine solution, and on the other end to a swivel (050-0022, Alice King Chatham, Hawthorne, CA) via Tygon tubing (1.52 mm o.d., 0.51 mm i.d.; Fisher Scientific, Springfield, NJ). The swivel attached to a tether (C313CS; Plastic Products, Roanoke, VA) that was then secured to the cannula in the harness. Rats were allowed to recover for 3 days before starting the self-administration portion of the study. During this time, they received daily injections of gentamicin (2.0 mg/kg, i.v.) and heparinized saline (0.3 cc, i.v.) to prevent infection and/or occlusion of the catheter.

2.4.4. Self-administration

2.4.4.1. Training. After recovery from surgery, rats were trained to self-administer i.v. cocaine (0.4 mg/kg/inf) in 2-h daily sessions (0900–1100 h). A fixed-ratio 1 (FR 1), 20-s timeout schedule of reinforcement was used. Responding on the active lever resulted in a cocaine infusion and illumination of the stimulus lights above the lever for 20 s. During this time, responses were counted but had no other consequence. Lever pressing on the inactive lever also illuminated the corresponding stimulus lights; however, there was no other programmed consequence. This was done so that conditions on both levers were the same except for the delivery of the drug. Thus, responding on the active lever was not an artifact of the conditioned reinforcing effects of the stimulus lights, rather it could be attributed to the presence of the drug and its reinforcing effects. To facilitate lever pressing during training, the active lever was initially baited with a small amount of peanut butter (<0.5 g) and rats were given two cocaine priming injections (i.v.) at the beginning of each training session. When rats self-administered ≥20 infusions/day for 3 days and exhibited active/inactive ratios ≥2:1, peanut butter and/or priming injections were discontinued.

2.4.4.2. Maintenance, extinction, and reinstatement. If lever pressing was maintained (≥20 infusions, active/inactive ratio ≥2:1) upon discontinuation of the priming injections, rats were then tested in a reinstatement procedure similar to that described by deVries et al. (1998), starting the following day. This procedure was selected because it employs an extended abstinence period and produces robust cocaine-induced reinstatement responding in rats (de Vries et al., 1998; Larson et al., 2005). Under this procedure, rats were allowed to lever press under a FR 1, 20-s timeout schedule for cocaine for 14 days during 2-h sessions beginning at 0900 h (*maintenance*). After maintenance, saline was substituted for cocaine and self-administration behavior extinguished over the next 21 days (*extinction*). During extinction, all other stimulus conditions remained the same; therefore, decreases in responding specifically reflected decreases in drug-seeking behavior due to the absence of cocaine reward (vs. loss of stimulus control due to the elimination of cocaine-associated cues). This methodology allows a slower extinction pattern with the potential for revealing group differences that are not obscured by a floor effect, as removal of the cues along with saline substitution tends to result in rapid and complete extinction of responding. Following extinction, drug pumps and stimulus lights were unplugged for 3 days to eliminate the potential for cue-mediated responding. After 3 days of extinction without cues, reinstatement testing commenced, again without cues. Testing consisted of 6 days of alternating noncontingent saline and cocaine (10 mg/kg, i.p.) priming injections. One injection, either saline (S) or cocaine (C), was given at the beginning of each 2-h session (0900 h), according to the following sequence: S C S C S C. Lever responding was counted, but had no consequence.

2.5. Data analysis

Mean locomotor activity during day 1 and day 2 of testing was analyzed with a two-way repeated measures ANOVA (group and time), and the mean overall activity during the sessions was analyzed using two-tailed student's *t*-tests. Mean daily wheel revolutions were analyzed using a two-way repeated measures ANOVA (group and day), and mean revolutions/day were analyzed with a one-tailed Student's *t*-test. Analysis of wheel running activity during the first and last 3 days of access was done using paired Student's *t*-tests. Mean locomotor activity after an acute saline or cocaine injection was analyzed with a three-way repeated measures ANOVA (priming injection type, group, and time), and the mean overall activity during these sessions was assessed by paired Student's *t*-tests (one-tailed, as cocaine-induced increases in locomotor activity were predicted). During maintenance and extinction, the mean infusions self-administered were assessed using two-way repeated measures ANOVAs (group and day). During reinstatement, within group responding on the active lever after saline- or cocaine-priming injection was analyzed by paired

Student's *t*-tests (one-tailed, as cocaine-induced increases in active lever responding were predicted). Comparisons of active and inactive lever responses during all phases were analyzed using two-way repeated measures ANOVAs. All analyses were conducted using GB Stat (Dynamic Microsystems, Inc., Silver Spring, MD). When appropriate, post-hoc comparisons were analyzed using Bonferroni corrected alpha-levels to control for type-I error inflation resulting from multiple contrasts. Separate two-tailed Student's *t*-tests were used for a priori group comparisons of cocaine-induced locomotor activity and cocaine-induced reinstatement of lever responding in HiR and LoR rats. Results were considered significant if $p<0.05$.

3. Results

3.1. Assessment of locomotor response to novelty and baseline locomotor activity

Fig. 2 illustrates the locomotor activity in the circular track across the 45-min testing period for the 2 days prior to wheel running exposure. Insets represent the mean (±S.E.M.) overall activity during this time. The upper frame shows the locomotor response to novelty (day 1) and the lower frame represents baseline locomotor activity (day 2) in rats that subsequently became HiR or LoR. On day 1, there was a significant effect of time [$F_{(8,125)}=54.92$, $p<0.05$], and both HiR and LoR rats' locomotor activity decreased across the 45-min testing period. During this time, there was a trend for higher locomotor activity in the novel environment in rats that subsequently became HiR compared to LoR rats (5/7 HiR rats were also high novelty responders); however, the effect did not reach statistical significance [$F_{(1,125)}=4.27$, $p=0.061$].

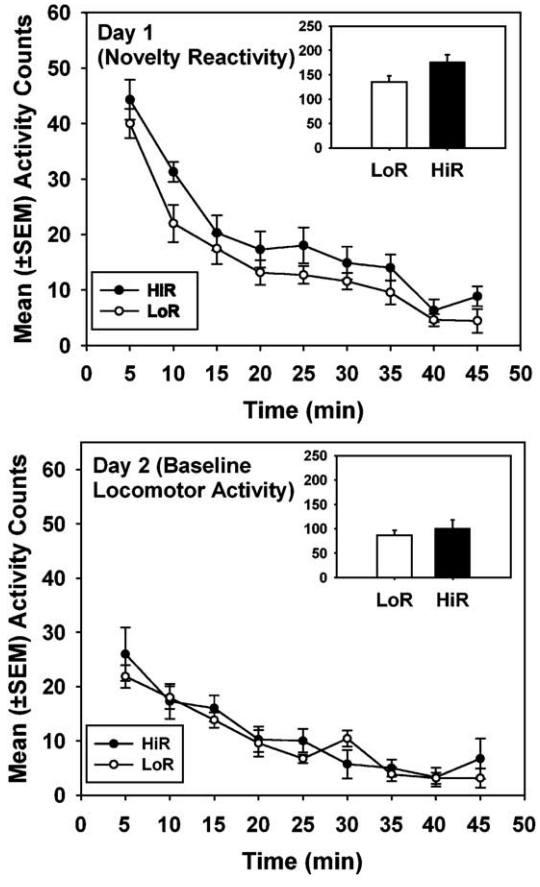

Fig. 2. Locomotor response to novelty (day 1, upper frame) and baseline locomotor activity (day 2, lower frame) are represented for HiR (closed circles) and LoR (open circles) rats. Each data point represents the mean (±S.E.M.) number of activity counts in 5-min intervals. The insets represent the mean (±S.E.M.) overall activity across the 45-min testing period.

Since there was a significant reduction in locomotor activity in the circular track from day 1 to day 2 ($t_{27}=4.24$, $p<0.05$), day 2 activity was analyzed independently and was considered to reflect baseline activity levels (Fig. 2, lower panel). Similar to day 1, locomotor activity in the circular track decreased across the 45-min testing period [$F_{(8,125)}=26.60$, $p<0.05$]. Analysis revealed no significant differences in locomotor activity between HiR and LoR rats on day 2 of testing.

3.2. Wheel running

After initial locomotor testing, rats were given access to the running wheels for 21 days, and the group was subsequently divided into HiR and LoR subgroups by a median split. Fig. 3 shows the wheel running patterns for HiR and LoR rats across the 21-day access phase. The inset depicts the mean wheel revolutions/day during this time. As expected by the selection process (median split), HiR rats ran on the wheels more than the LoR rats ($t_{13}=-4.16$, $p<0.05$). Mean (±S.E.M.) revolutions/day were 336.0±50.4 (range 104.0–505.5 rev/day) for LoR rats and 1238.8±211.0 (range 701.5–1984.3 rev/day) for HiR rats. Analysis of wheel running activity across the 21 days revealed a group effect [$F_{(1,293)}=22.86$, $p<0.05$], a day effect [$F_{(20,293)}=5.80$, $p<0.05$], and a group × day interaction [$F_{(20,293)}=4.87$, $p<0.05$]. Post-hoc analyses (Bonferroni) showed that HiR rats had more wheel revolutions than LoR rats on days 15, 17, 19, 20, and 21. Paired *t*-tests of wheel running activity in the beginning (days 1–3) and end (days 19–21) of wheel access revealed that HiR rats escalated their wheel running across the 21-day access period, as indicated by a significant increase in wheel revolutions during the final 3 days compared to the first 3 days ($t_6=-3.62$, $p<0.05$). Conversely, LoR rats maintained more steady levels of wheel running over the 21-day access period, and they did not show significant changes from the first to the last 3 days.

As wheel running can affect feeding (Afonso and Eikelboom, 2003), and differential food intake can influence subsequent drug self-administration (Carroll, 1999), food intake, water intake, and body weights during the wheel running phase were also analyzed to determine whether HiR and LoR rats differed on these measures. Analyses revealed no significant differences in food and water intake or body weight during the wheel running phase of the experiment. HiR and LoR groups consumed a mean of 23.87 (±1.8) and 24.82 (±2.3) g food/day, and they consumed an average of 35.96 (±2.6) and 35.78 (±2.6) ml water/day, respectively. Rat weights varied some during wheel running, but there were no significant differences in weights between HiR and LoR groups (285.82±2.4 and 287.75±9.4 g, respectively).

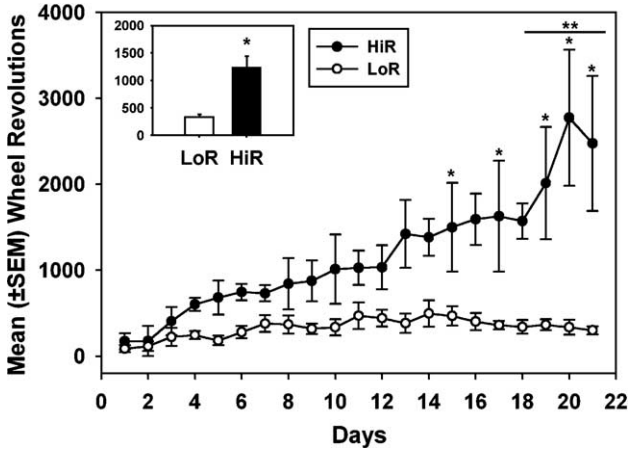

Fig. 3. Mean (±S.E.M.) daily wheel revolutions for HiR (closed circles) and LoR (open circles) rats during the wheel access phase. The inset depicts the mean (±S.E.M.) wheel revolutions/day during this phase. Asterisks indicate days where HiR rats ran more than LoR rats ($p<0.05$). The double asterisks over the bar represent that the final 3 days of wheel running were significantly greater than the first 3 days of wheel running in HiR rats ($p<0.05$).

3.3. Locomotor response to acute cocaine administration

The upper panel of Fig. 4 illustrates locomotor activity in the circular track for the 45-min after a priming injection of saline (day 31) or 10 mg/kg cocaine (day 32) for HiR and LoR rats. Mean (±SEM) overall activity during these sessions is depicted in the lower panel. A three-way repeated measures ANOVA revealed that rats had more locomotor activity after cocaine than saline [$F_{(1,251)}=7.97$, $p<0.05$] and that activity decreased as a function of time [$F_{(8,251)}=24.23$, $p<0.05$]. There was no group effect, and no group × time nor priming injection type × group × time interaction; however, there was a priming injection type × time interaction [$F_{(8,251)}=3.45$, $p<0.05$]. Paired *t*-tests of the overall activity during the 45-min sessions revealed that locomotor activity was increased after cocaine as compared to saline in the LoR, but not the HiR group. Furthermore, a two-tailed *t*-test of the locomotor activity after cocaine showed no significant group differences; thus, the a priori hypothesis that HiR rats would have greater cocaine-induced locomotor activity than LoR rats was not supported by the data.

3.4. Self-administration

There were no significant differences in the number of training days needed to produce criterion cocaine self-administration (≥20 inf/day) in HiR (24.86±7.6) and LoR (17.86±5.7) rats. Fig. 5 shows the mean (±S.E.M.) number of cocaine infusions self-administered across the 14-day maintenance period, and the mean (±S.E.M.) infusions/session are shown in the inset. A repeated-measures ANOVA revealed a significant group effect [$F_{(1,195)}=5.512$, $p<0.05$], indicating that HiR rats self-administered more cocaine infusions than LoR rats during maintenance. Although the number of cocaine infusions self-administered each day was higher in HiR compared to LoR rats, post-hoc analyses (Bonferroni) revealed

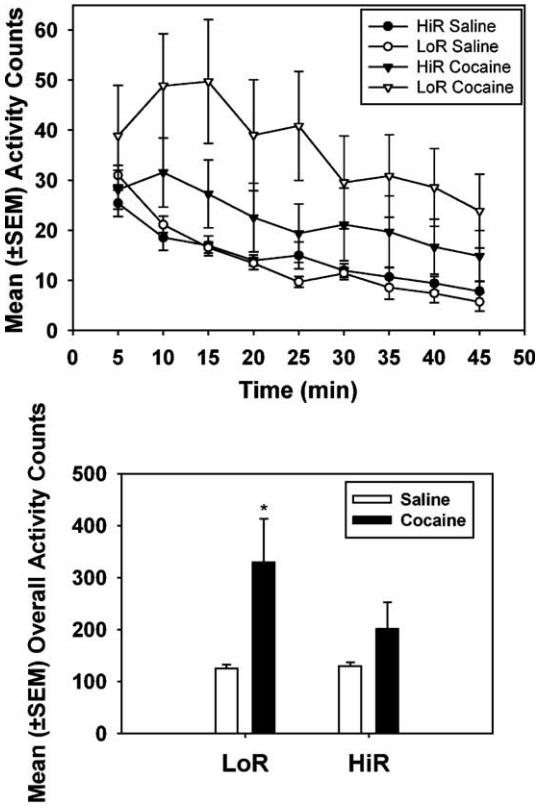

Fig. 4. The upper frame depicts the locomotor response to a priming injection of saline (circles) or 10 mg/kg cocaine (triangles) for HiR (closed symbols) and LoR (open symbols) rats. Each data point represents the mean (±S.E.M.) number of activity counts in 5-min intervals. The lower frame illustrates the mean (±S.E.M.) overall locomotor activity across the 45-min testing period for HiR and LoR rats after saline (open bars) or cocaine (closed bars). *$p<0.05$ cocaine vs. saline in the LoR group.

that this was not significant on any particular day. There were no group differences in inactive lever pressing, and responding was higher on the active lever than the inactive lever for both HiR [$F_{(1,195)}=11.59$, $p<0.05$] and LoR [$F_{(1,195)}=262.31$,

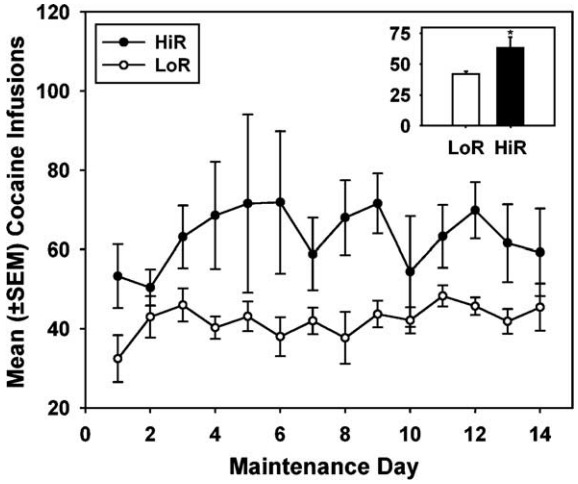

Fig. 5. The mean (±S.E.M.) number of cocaine infusions self-administered across the 14-day maintenance period are shown for HiR (closed circles) and LoR (open circles) rats. The mean (±S.E.M.) infusions self-administered/session are shown in the inset. *$p<0.05$ HiR vs. LoR.

$p<0.05$] rats. There was no escalation of cocaine self-administration under the limited access conditions (2-h sessions), as indicated by the lack of a day effect on the number of infusions self-administered. Also, there was no treatment × day interaction.

3.5. Cocaine-seeking behavior during extinction

Fig. 6 shows the mean (±S.E.M.) number of saline infusions self-administered across the 21-day extinction period. The inset represents the mean (±S.E.M.) saline infusions self-administered/session. Both HiR and LoR rats extinguished their self-administration behavior across the 21 days, as indicated by a significant day effect [$F_{(20,293)}=14.84$, $p<0.05$] and the low-stable responding over the last 4 days. However, there were no group differences between HiR and LoR rats for saline self-administration across the extinction phase and no group × day interaction. Similarly, there were no group differences in inactive lever responding during this phase (data not shown).

3.6. Cocaine-seeking behavior during reinstatement

Fig. 7 depicts the mean (±S.E.M.) number of responses on the active lever following priming injections of saline or cocaine during reinstatement testing in HiR and LoR rats. There were no group differences in responding on the active lever after priming injections of saline, and both HiR ($t_6=-2.34$, $p<0.05$) and LoR rats ($t_6=-6.75$, $p<0.05$) increased their responding on the active lever after cocaine priming injections. In support of the a priori hypothesis, a two-tailed t-test revealed that reinstatement of active lever responding was greater in HiR compared to LoR rats ($t_{12}=-5.87$, $p<0.05$). Compared to when they were given saline priming injections, HiR rats had a 7.1-fold increase in their active lever pressing after cocaine priming injections, while LoR rats only had a 3.2-fold increase. There were no group differences in inactive lever responding after saline or cocaine priming injections (data not shown). Inactive lever pressing was higher after cocaine than saline priming injections [$F_{(1,55)}=10.45$, $p<0.05$]; however, post-hoc analysis showed that active lever responding was higher than inactive lever pressing on cocaine ($p<0.05$), but not on saline days.

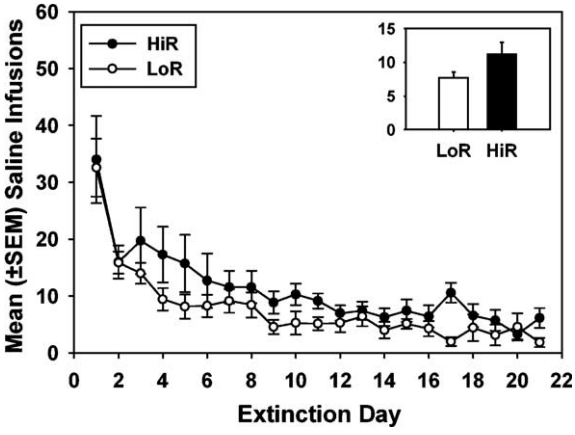

Fig. 6. Mean (±S.E.M.) number of saline infusions self-administered during the 21-day extinction period is shown for HiR (closed circles) and LoR (open circles) rats. The inset depicts the mean (±S.E.M.) infusions self-administered/session during this phase.

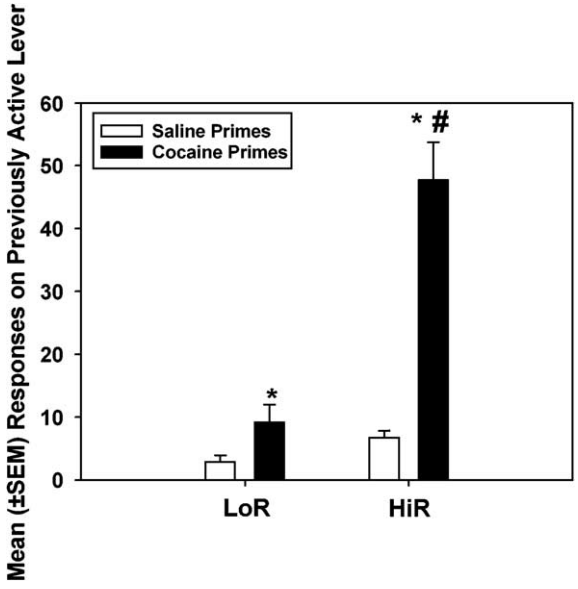

Fig. 7. Reinstatement of cocaine-seeking behavior after priming injections of saline (open bars) or 10 mg/kg cocaine (closed bars) for HiR and LoR rats. Bars represent the mean (±S.E.M.) number of responses on the previously active lever. Asterisks represent a significant increase in lever responding after cocaine primes compared to saline primes ($p<0.05$). The pound symbol represents that HiR rats had significantly more responses after cocaine primes than LoR rats ($p<0.05$).

3.7. Cocaine self-administration and cocaine-seeking behavior in high and low novelty responders

Although it was not an aim of the present study to examine the relationship between novelty responding and subsequent cocaine-mediated behaviors during different phases of drug abuse, nor was it originally planned to determine the relationship between novelty responding and wheel running, interesting relationships emerged and were considered. We conducted an analysis of the data when rats were divided (via a median split) into high and low novelty groups. We found no significant differences between these groups in their cocaine-induced locomotor activity, cocaine self-administration in maintenance, or cocaine-seeking behavior during extinction. However, a significant difference was found between high and low responders to novelty in cocaine-seeking behavior during reinstatement. That is, high novelty responders had a significantly greater number of responses on previously active lever than low responders after cocaine priming injections ($t_{12}=-2.42$, $p<0.05$, data not shown).

4. Discussion

The goal of the present study was to test the hypothesis that higher (vs. lower) rates of wheel running are subse-

quently associated with elevated cocaine-induced locomotor activity, as well as maintenance, extinction, and reinstatement of cocaine-seeking behavior. We found that, compared to LoR rats, HiR rats had greater cocaine self-administration during maintenance and more cocaine-induced reinstatement of lever responding than LoR rats. These differences seem to reflect differences in wheel running avidity in HiR and LoR rats, as rats did not differ in their locomotor response in a novel environment or in their basal locomotor activity. The results presented here indicated that individual differences in wheel running predicted the subsequent vulnerability for cocaine self-administration and reinstatement in rats. It also suggests that HiR rats are more motivated for cocaine-seeking during ongoing self-administration, as well as under extended abstinence conditions (reinstatement).

Contrary to what was hypothesized, HiR rats were not more sensitive than LoR rats to the locomotor-activating effects of cocaine. Although the results shown in Fig. 4 suggest that HiR rats may have actually been *less* sensitive to cocaine's locomotor-activating effects than LoR rats, analysis revealed no statistically significant differences between HiR and LoR groups in their locomotor response to acute cocaine administration. This result was unexpected, and is not consistent with previous studies that compared high and low responders for novelty (Piazza et al., 1989; Sell et al., 2005) or sugar intake (Sills and Vaccarino, 1994); however, the ability to predict sensitivity to the psychomotor effects of stimulants in high and low responders may be dependent on the behavior being examined (e.g., wheel running, novelty, etc.). It may also depend on the hormonal state in females at the time of testing (Sell et al., 2005), which was not measured or controlled in our study. Furthermore, much of the previous work examining differences between high and low responders has been conducted in male rats. Since female rats generally show greater drug-mediated behavior than males (Roth et al., 2004), it is possible that the present results were influenced by a ceiling effect in the females.

While greater avidity for wheel running in HiR rats was not associated with an enhanced response to the locomotor activating effects of cocaine, it was associated with enhanced cocaine self-administration during maintenance. As hypothesized, HiR rats self-administered more cocaine infusions than LoR rats, which is consistent with other studies showing that high responders (to nondrug events) are more vulnerable to the self-administration of drugs of abuse compared to low responders (e.g., Piazza et al., 1990, 1991; Gosnell et al., 1995; Dess et al., 1998; Carroll et al., 2002). Together, these findings suggest that a predisposition for behaviors mediated by nondrug rewards is associated with enhanced vulnerability for drug abuse, and individuals that are high responders for nondrug rewards are more motivated than low responders to self-administer psychostimulant drugs such as cocaine.

It is possible that both the increased, escalated levels of wheel running and higher levels of cocaine self-administration in maintenance shown in HiR compared to LoR rats may reflect a relative decrease in reward function in these animals. Both wheel running (Afonso and Eikelboom, 2003) and cocaine self-administration (Lynch and Carroll, 2001) are self-regulated behaviors; thus, increased performance may reflect an attempt to compensate for tolerance to the rewarding aspects of these behaviors. For example, LoR rats had lower, steady levels of wheel running across the 21-day access phase, while HiR rats more elevated and escalated (increasing over time) patterns of wheel running activity. Escalation of drug self-administration is a key feature of drug addiction, and escalation has been shown to increase the subsequent motivation to take drugs, presumably due to reward tolerance, or a decrease in reward function (Ahmed and Koob, 1998, 1999). Escalation is usually discussed in terms of drug self-administration; however, it is apparent from the present results and others (Lattanzio and Eikelboom, 2003; Colantuoni et al., 2001) that escalation is a phenomenon that may occur with nondrug rewards such as wheel running and glucose intake, respectively. Therefore, HiR rats may have escalated their wheel running over time in order to compensate for decreased hedonic effects; thus, these rats may have been relatively "reward addicted" even prior to their drug exposure. Thus, when allowed to self-administer cocaine, HiR may have needed to consume more cocaine than LoR rats in order to achieve similar effects. However, HiR rats may have also self-administered more cocaine in maintenance to compensate for higher levels of deprivation of the wheel reward (or reward contrast), which would be consistent with other findings of increased drug self-administration during deprivation from nondrug reward access (Carroll and Boe, 1982).

While no group differences were found in cocaine-seeking (saline self-administration) behavior during extinction, avidity for wheel running predicted cocaine-seeking behavior during reinstatement, as HiR rats had more cocaine-induced reinstatement of lever responding than LoR rats. To our knowledge, this is the first study to show that wheel running predicts vulnerability to the reinstatement of drug-seeking behavior after an extended abstinence period. These and other data suggest that high responders may be more motivated for cocaine-seeking than low responders under multiple conditions (e.g., acquisition, maintenance, reinstatement). Similar to what was discussed for cocaine self-administration in maintenance, it is possible that the escalation of wheel running in HiR rats influenced subsequent reinstatement responding in these animals, which is consistent with studies that show escalation to be associated with enhanced reinstatement of drug-seeking behavior (Ahmed and Koob, 1998; Ahmed et al., 2000). However, it is also possible that HiR rats had greater reinstatement of cocaine-seeking behavior because they were more sensitive to the incentive-motivational properties of cocaine. Robinson and Berridge (1993) have proposed that, upon continued drug use, the incentive value of drugs and their associated stimuli (e.g., cues) are enhanced, leading to increased motivation for drug-seeking and drug-taking behavior. Sensitization of brain reward systems is thought to persist even after long abstinence periods, and similar to escalation, sensitization has been associated with an increased propensity for reinstatement of drug-seeking after re-exposure to cocaine

(deVries et al., 1998, 2002). However, it is important to note that the mechanisms underlying reinstatement behavior are still poorly understood, and differences between HiR and LoR rats may reflect other processes besides incentive-salience (e.g., incentive learning).

A potential weakness of the present study was that we used only one dose of cocaine (10 mg/kg) to assess the psychomotor and motivational effects of cocaine, and we were not able to generate dose–effect functions to specifically assess the relative reinforcing effects of cocaine in HiR and LoR rats. Thus, we cannot make any definitive conclusions about whether the enhanced motivation for cocaine seeking was due to rats overcoming a reduced hedonic value of cocaine (caused by escalation of wheel running) or due to an increase in the incentive-salience of cocaine (caused by sensitization of brain reward). Examination of multiple doses would have greatly increased the length of this study, and it would have required counterbalancing dose order, which could have been differentially affected in HiR and LoR rats. Therefore, we chose to examine only one (10 mg/kg) dose as it is at the peak of the dose–response curve for cocaine-induced reinstatement of lever responding in rats (Schenk and Partridge, 1999), and it produces significant, but not maximal increases in locomotor activity in rats (Sell et al., 2000; Antoniou et al., 1998). Other studies that have examined dose–response functions for high and low responders on nondrug measures have typically found that dose–response curves are shifted upward in high compared to low responders (e.g., Dess et al., 1998; Piazza et al., 2000; Brennan et al., 2001; DeSousa et al., 2000). This indicates that high responders may not be more tolerant or sensitive to the psychomotor or rewarding effects of drugs, but they are more motivated to consume drugs than low responders at all doses tested.

Another consideration is that the higher reinstatement in HiR rats was not due to a vulnerable phenotype in these animals, but rather was the product of higher cocaine consumption during maintenance. This would be consistent with Sutton et al. (2000) who found that the level of cocaine intake during self-administration was the strongest indicator of cocaine seeking behavior during abstinence (i.e., extinction and reinstatement). However, while HiR rats had increased cocaine-seeking behavior during reinstatement testing, they did not differ from LoR rats in their cocaine-seeking behavior during extinction. Thus, differences in reinstatement do not appear to be a result of differential cocaine intake in maintenance. Furthermore, as extinction responding may reflect impulsiveness more than the propensity for compulsive drug intake (Shaham et al., 2000; Jentsch and Taylor, 2001), the lack of group differences in extinction also suggests that differences in impulsivity did not underlie the differential reinstatement behavior seen in HiR and LoR rats.

Interestingly, we found no differences in cocaine-induced locomotor activity, cocaine self-administration in maintenance, or cocaine-seeking behavior during extinction when rats were separated into high and low response groups based on their locomotor activity in a novel environment. This was surprising, as higher responses to novelty are typically associated with enhanced psychomotor responses and self-administration of stimulant drugs (e.g., Piazza et al., 1989, 1990, 2000; Klebaur and Bardo, 1999; Sell et al., 2005). However, locomotor differences after acute stimulant administration in high and low novelty responders are not always found (Pierre and Vezina, 1997; Djano and Martin-Iverson, 2000; Hooks et al., 1991; Klebaur and Bardo, 1999), and novelty effects are not typically seen when rats self-administer higher cocaine doses (Mantsch et al., 2001; Sutton et al., 2000). Procedural differences may also account for the lack of an effect of novelty in the present study. For example, Sell et al. (2005) reported higher cocaine-induced locomotor activity in female rats that were high responders to novelty compared to those that were low responders to novelty. However, the upper and lower 15% of the group was used for their analyses, while in the present study we used a median split to divide rats into high and low responding groups, which may have minimized differences. Also, due to the goals of the study, we imposed an extended period of wheel access in between the assessment of novelty responding and the assessment of cocaine-mediated behaviors (i.e., locomotor activity, self-administration, reinstatement), while in previous studies the behavioral assessments were made shortly after the high/low novelty assessment. It is also possible that novelty and wheel running interacted in some way that obscured an observable effect of novelty. This potential interaction between novelty and wheel running may furthermore be dependent on the measure being examined. For example, while neither wheel running or novelty predicted cocaine-induced locomotor activity, wheel running alone predicted self-administration behavior in maintenance, and both novelty-responding and wheel running predicted cocaine-seeking behavior during reinstatement.

In summary, the present study suggests that HiR rats were more vulnerable than LoR rats to self-administer cocaine and to reinstate cocaine-seeking induced by priming injections of cocaine. However, avidity for wheel running did not significantly affect cocaine-induced increases in locomotor activity. The finding of group differences in maintenance and reinstatement, but not during extinction, is consistent with work of Deroche-Gamonet et al. (2004), who suggests that the underlying constructs for extinction and those for addictive-like behaviors (e.g., motivation, drug-seeking, resistance to punishment) are different and largely independent. Overall, these findings indicate that, compared with LoR rats, HiR rats were more motivated for cocaine-seeking, but were not necessarily more sensitive to the locomotor-activating effects of cocaine. The results found during maintenance and cocaine-induced reinstatement suggest that factors related to the vulnerability to self-administer drugs may also impact the vulnerability to addiction and relapse. Given the rewarding nature of wheel running, and the finding that HiR rats escalated their wheel running during the 21-day access phase, while LoR rats did not, it could be concluded that some animals may be predisposed to reward-seeking in general. These results may lead to screening methods for identifying at-risk human drug users, and it may aid in developing prevention strategies based on specific vulnerabilities.

Acknowledgements

The authors would like to thank Justin Anker, Jon German, Nate and Nick Cmiel for their technical assistance with the experiments, and Dr. Jennifer Newman, Marissa Anderson, Justin Anker, Jen Perry, and Joey Thorne for critically reviewing the manuscript. This research was supported by NIDA grants R01 DA03240 and K05 DA15267 (M.E.C.).

References

Afonso VM, Eikelboom R. Relationship between wheel running, feeding, drinking, and body weight in male rats. Physiol Behav 2003;80(1):19–26.

Ahmed SH, Koob GF. Transition from moderate to excessive drug intake: change in hedonic set point. Science 1998;282(5387):298–300.

Ahmed SH, Koob GF. Long-lasting increase in the set point for cocaine self-administration after escalation in rats. Psychopharmacology (Berl) 1999; 146(3):303–12.

Ahmed SH, Walker JR, Koob GF. Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology 2000;22(4):413–21.

Antoniou K, Kafetzopoulos E, Papadopoulou-Daifoti Z, Hyphantis T, Marselos M. D-Amphetamine, cocaine and caffeine: a comparative study of acute effects on locomotor activity and behavioural patterns in rats. Neurosci Biobehav Rev 1998;23(2):189–96.

Brennan K, Roberts DC, Anisman H, Merali Z. Individual differences in sucrose consumption in the rat: motivational and neurochemical correlates of hedonia. Psychopharmacology (Berl) 2001;157(3):269–76.

Carroll ME. The role of food deprivation in the maintenance and reinstatement of cocaine-seeking behavior in rats. Drug Alcohol Depend 1985;16(2): 95–109.

Carroll ME, Boe IN. Increased intravenous drug self-administration during deprivation of other reinforcers. Pharmacol Biochem Behav 1982;17(3): 563–7.

Carroll ME. Interactions between food and addiction. In: Niesink RJM, Hoefakker RE, Westera W, Jaspers RMA, Kornet LMW, Boobis S, editors. Neurobehavioral Toxicology and Addiction: Food, Drugs, and Environment. Boca Raton, FL: CRC Press; 1999. p. 286–311.

Carroll ME, Morgan AD, Lynch WD, Campbell UC, Dess NK. Intravenous cocaine and heroin self-administration in rats selectively bred for differential saccharin intake: phenotype and sex differences. Psychopharmacology (Berl) 2002;161(3):304–13.

Carroll ME, Bickel WK, Higgins ST. Nondrug incentives to treat drug abuse: laboratory and clinical developments. In: Carroll ME, Ovemier JB, editors. Animal Research and Human Psychological Health: Advancing Human Welfare Through Behavioral Science. Washington, DC: American Psychological association; 2001. p. 138–54.

Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, Schwartz GJ, et al. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. Neuroreport 2001;12(16):3549–52.

Deroche-Gamonet V, Belin D, Piazza PV. Evidence for addiction-like behavior in the rat. Science 2004;305(5686):1014–7.

DeSousa NJ, Bush DE, Vaccarino FJ. Self-administration of intravenous amphetamine is predicted by individual differences in sucrose feeding in rats. Psychopharmacology (Berl) 2000;148(1):52–8.

Dess NK, Badia-Elder NE, Thiele TE, Kiefer SW, Blizard DA. Ethanol consumption in rats selectively bred for differential saccharin intake. Alcohol 1998;16(4):275–8.

de Vries TJ, Schoffelmeer ANM, Binnekade R, Mulder AH, Vanderschuren LJMJ. Drug-induced reinstatement of heroin- and cocaine-seeking behaviour following long-term extinction is associated with expression of behavioural sensitization. Eur J Neurosci 1998;10(11):3565–71.

de Vries TJ, Schoffelmeer AN, Binnekade R, Raaso H, Vanderschuren LJ. Relapse to cocaine- and heroin-seeking behavior mediated by dopamine D2 receptors is time-dependent and associated with behavioral sensitization. Neuropsychopharmacology 2002;26(1):18–26.

Djano S, Martin-Iverson MT. Does locomotor response to novelty in rats predict susceptibility to develop sensitization to cocaine and PHNO? Behav Pharmacol 2000;11(6):455–70.

Eckel LA, Houpt TA, Geary N. Spontaneous meal patterns in female rats with and without access to running wheels. Physiol Behav 2000;70(3–4): 397–405.

Finger F. The effect of food deprivation and subsequent satiation upon general activity in the rat. J Comp Physiol Psychol 1951;44(6):557–64.

Gosnell BA. Sucrose intake predicts rate of acquisition of cocaine self-administration. Psychopharmacology (Berl) 2000;149(3):286–92.

Gosnell BA, Krahn DD. The relationship between saccharin and alcohol intake in rats. Alcohol 1992;9(3):203–6.

Gosnell BA, Lane KE, Bell SM, Krahn DD. Intravenous morphine self-administration by rats with low versus high saccharin preferences. Psychopharmacology (Berl) 1995;117(2):248–52.

Hitchcock FA. Studies in vigor: V The comparative activity of male and female albino rats. Am J Physiol 1925;75:205–10.

Homberg JR, van den Akker M, Raaso HS, Wardeh G, Binnekade R, Schoffelmeer AN, de Vries TJ. Enhanced motivation to self-administer cocaine is predicted by self-grooming behaviour and relates to dopamine release in the rat medial prefrontal cortex and amygdala. Eur J Neurosci 2002;15(9):1542–50.

Hooks MS, Jones GH, Smith AD, Neill DB, Justice JB. Individual differences in locomotor activity and sensitization. Pharmacol Biochem Behav 38(2):467–70.

Iversen IH. Techniques for establishing schedules with wheel running as reinforcement in rats. J Exp Anal Behav 1993;60(1):219–38.

Jentsch DJ, Taylor JR. Impaired inhibition of conditioned responses produced by subchronic administration of phencyclidine to rats. Neuropsychopharmacology 2001;24(1):66–74.

Jones LC, Bellingham WP, Ward LC. Sex differences in voluntary locomotor activity of food-restricted and ad libitum-fed rats Implications for the maintenance of a body weight set-point. Comp Biochem Physiol A 1990; 96(2):287–90.

Kampov-Polevoy AB, Overstreet DH, Rezvani AH, Jonowsky DS. Saccharin-induced increase in daily fluid intake as a predictor of voluntary alcohol intake in alcohol-preferring rats. Physiol Behav 1995;57(4):791–5.

Kent S, Hurd M, Satinoff E. Interactions between body temperature and wheel running over the estrous cycle in rats. Physiol Behav 1991;49(6):1079–84.

Klebaur JE, Bardo MT. Individual differences in novelty seeking on the playground maze predict amphetamine conditioned place preference. Pharmacol Biochem Behav 1999;63(1):131–6.

Klebaur JE, Bevins RA, Segar TM, Bardo MT. Individual differences in behavioral responses to novelty and amphetamine self-administration in male and female rats. Behav Pharmacol 2001;12(4):267–75.

Krasnoff A, Weston LM. Pubertal status and sex differences: activity and maze behavior in rats. Dev Psychobiol 1976;9(3):261–9.

Larson EB, Roth ME, Anker JJ, Carroll ME. Effect of short- vs. long-term estrogen on reinstatement of cocaine-seeking behavior in female rats. Pharmacol Biochem Behav 2005;82(1):98–108.

Lattanzio SB, Eikelboom R. Wheel access duration in rats: I Effects on feeding and running. Behav Neurosci 2003;117(3):496–504.

Lett BT, Grant VL, Byrne MJ, Koh MT. Pairing of a distinctive chamber with the aftereffect of wheel running produce conditioned place preference. Appetite 2000;34(1):87–94.

Lett BT, Grant VL, Koh MT, Flynn G. Prior experience with wheel running produces cross-tolerance to the rewarding effects of morphine. Pharmacol Biochem Behav 2002;72(1–2):101–5.

Lynch WJ, Carroll ME. Sex differences in the acquisition of intravenously self-administered cocaine and heroin in rats. Psychopharmacology (Berl) 1999; 144(1):77–82.

Lynch WJ, Carroll ME. Regulation of drug intake. Exp Clin Psychopharmacol 2001;9(2):131–43.

Lynch WJ, Roth ME, Mickelberg JL, Carroll ME. Role of estrogen in the acquisition of intravenously self-administered cocaine in female rats. Pharmacol Biochem Behav 2001;68(4):641–6.

Mantsch JR, Ho A, Schlussman SD, Kreek MJ. Predictable individual differences in the initiation of cocaine self-administration by rats under

extended-access conditions are dose-dependent. Psychopharmacology (Berl) 2001;157(1):31–9.
Morgan MA, Pfaff DW. Estrogen's effects on activity, anxiety, and fear in two mouse strains. Behav Brain Res 2002;132(1):85–93.
National Research Council DW. Guide for the care and use of mammals in neuroscience and behavioral research. Washington: The National Academics; 2003.
Perry JL, Larson EB, German JP, Madden GJ, Carroll ME. Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. Psychopharmacology (Berl) 2005;178(2–3):193–201.
Piazza PV, Le Moal ME. Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. Annu Rev Pharmacol Toxicol 1996;36:359–78.
Piazza PV, Le Moal ME. The role of stress in drug self-administration. Trends Pharmacol Sci 1998;19(2):67–74.
Piazza PV, Deminiere JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. Science 1989;245(4925):1511–3.
Piazza PV, Deminiére JM, Maccari S, Morméde P, Le Moal M, Simon H. Individual reactivity to novelty predicts probability of amphetamine self-administration. Behav Pharmacol 1990;1(4):339–45.
Piazza PV, Maccari S, Deminiére JM, Le Moal M, Morméde P, Simon H. Corticosterone levels determine individual vulnerability to amphetamine self-administration. Proc Natl Acad Sci U S A 1991;88(6):2088–92.
Piazza PV, Deroche-Gamonent V, Rouge-Pont F, Le Moal M. Vertical shifts in self-administration dose–response functions predict a drug-vulnerable phenotype predisposed to addiction. J Neurosci 2000;20(11):4226–32.
Pierre PJ, Vezina P. Predisposition to self-administer amphetamine: the contribution of response to novelty and prior exposure to the drug. Psychopharmacology (Berl) 1997;129(3):277–84.
Poulos CX, Le AD, Parker JL. Impulsivity predicts individual susceptibility to high levels of alcohol self-administration. Behav Pharmacol 1995;6(8):810–4.
Robinson TE, Berridge TC. The neural basis of drug craving: an incentive sensitization theory of addiction. Brain Res Rev 1993;18(3):247–91.
Rodier WI. Progesterone–estrogen interactions in the control of activity-wheel running in the female rat. J Comp Physiol Psychol 1971;74(3):365–73.
Roth ME, Cosgrove KP, Carroll ME. Sex differences in the vulnerability to drug abuse: a review of preclinical studies. Neurosci Biobehav Rev 2004;28(6):533–46.
Schenk S, Partridge B. Cocaine-seeking produced by experimenter-administered drug injections: dose–effect relationships in rats. Psychopharmacology (Berl) 1999;147(3):285–90.
Sell SL, Scalzitti JM, Thomas ML, Cunningham KA. Influence of ovarian hormones and estrous cycle on the behavioral response to cocaine in female rats. J Pharmacol Exp Ther 2000;293(3):879–86.
Sell SL, Dillon AM, Cunningham KA, Thomas ML. Estrous cycle influence on individual differences in the response to novelty and cocaine in female rats. Behav Brain Res 2005;161(1):69–74.
Shaham Y, Erb S, Stewart J. Stress-induced relapse to heroin and cocaine seeking in rats: a review. Brain Res Rev 2000;33(1):13–33.
Sherwin CM. Voluntary wheel running: a review and novel interpretation. Anim Behav 1998;56(1):11–27.
Sills TL, Vaccarino FJ. Individual differences in sugar intake predict the locomotor response to acute and repeated amphetamine administration. Psychopharmacology (Berl) 1994;116(1):1–8.
Steiner M, Katz RJ, Carroll BJ. Detailed analysis of estrous-related changes in wheel running and self-stimulation. Physiol Behav 1982;28(1):201–4.
Sutton MA, Karanian DA, Self DW. Factors that determine a propensity for cocaine-seeking behavior during abstinence in rats. Neuropsychopharmacology 2000;22(6):626–41.
Werme M, Lindholm S, Thoren P, Franck J, Brene S. Running increases ethanol preference. Behav Brain Res 2002;133(2):301–8.