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Exercise to reduce the escalation of cocaine self-administration in adolescent and adult rats

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Abstract

Rationale—Concurrent access to an exercise wheel decreases cocaine self-administration under short access (5 h/day for 5 days) conditions and suppresses cocaine-primed reinstatement in adult rats.

Objective—The effect of exercise (wheel running) on the escalation of cocaine intake during long access (LgA, 6 h/day for 26 days) conditions was evaluated.

Methods—Adolescent and adult female rats acquired wheel running, and behavior was allowed to stabilize for 3 days. They were then implanted with an iv catheter and allowed to self-administer cocaine (0.4 mg/kg, iv) during 6-h daily sessions for 16 days with concurrent access to either an unlocked or a locked running wheel. Subsequently, for ten additional sessions, wheel access conditions during cocaine self-administration sessions were reversed (i.e., locked wheels became unlocked and vice versa).

Results—In the adolescents, concurrent access to the unlocked exercise wheel decreased responding for cocaine and attenuated escalation of cocaine intake irrespective of whether the locked or unlocked condition came first. However, cocaine intake increased when the wheel was subsequently locked for the adolescents that had initial access to an unlocked wheel. Concurrent wheel access either before or after the locked wheel access did not reduce cocaine intake in adults.

Conclusions—Wheel running reduced cocaine intake during LgA conditions in adolescent but not adult rats, and concurrent access to the running wheel was necessary. These results suggest that exercise prevents cocaine seeking and that this effect is more pronounced in adolescents than adults.

Keywords

Adolescence; Cocaine; Escalation; Exercise; Individual differences; Self-administration; Wheel running

Introduction

In animal research, exercise has been studied as an environmental enrichment that reduces drug abuse, and results are similar to those obtained with other environmental enhancements such as preferred dietary substances (Campbell and Carroll 2000; Carroll et al. 2008, 2009), social access (Bardo et al. 2001; Schenk et al. 1987), and novel stimuli (Bardo et al. 2001; Klebauer et al. 2001). Concurrent access to exercise reduced the maintenance of drug self-administration (Cosgrove et al. 2002; Miller et al. 2012) and reinstatement of drug-seeking behavior (Zlebnik et al. 2010). A history of exercise (Smith et al. 2008, 2011, 2012; Smith and Pitts 2011) or sequentially scheduled exercise (Lynch et al. 2010; Smith et al. 2008, 2011, 2012; Smith and Pitts 2011) also reduced acquisition, escalation, and reinstatement of cocaine-seeking behavior.

Vulnerability to drug abuse has been recently investigated in animal studies by examining individual differences in behavior directed toward nondrug rewards (Anker and Carroll 2011; Carroll et al. 2008, 2009, 2010; Flagel et al. 2008). For example, individual differences in sweet intake (high > low), impulsivity (high > low), and novelty seeking (high > low) have been associated with high and low drug seeking, respectively, during several phases of the addiction process including acquisition, maintenance, escalation, and reinstatement. In addition, biological variables such as sex (female > male) and age (adolescents > adults) add to the behavioral vulnerability factors to increase the severity of drug-seeking behavior (Carroll et al. 2008, 2009, 2010). For example, adolescents and adults were compared in numerous studies of drug abuse involving both the rewarding and aversive effects of drugs at several phases of drug abuse that are modeled in animals (see reviews by Schramm-Sapota et al. 2009; Spear 2000a, b, 2009, 2011). These findings indicated that while adolescents are more sensitive to the rewarding effects of drugs, they were also more resilient to the aversive effects. Other studies indicated that adolescents (vs. adults) have higher sweet preference (Friemel et al. 2010; Vaidya et al. 2004; Desor and Beauchamp 1987; but see Wilmouth and Spear 2009) and impulsivity (Vaidya et al. 2004; Desor and Beauchamp 1987; Anker et al. 2011), two additional vulnerability factors that predict drug abuse. However, to date little is known from clinical studies or preclinical animal studies of drug abuse with respect to how age and other individual differences are related to the efficacy of a behavioral or pharmacological treatment for drug abuse.

Animals given long access (LgA) to drugs exhibit “binge” patterns of intake with overall intake increasing steadily over 10–20 days (e.g., Ahmed and Koob 1998, 2005). Escalation is considered to be a critical phase in the transition from controlled drug use to uncontrolled use and addiction, and it is mediated by dramatic shifts in mesolimbic reward system functioning (Koob and Volkow 2010). While this translational animal model of binge drug use is sensitive to individual differences such as sex (Roth and Carroll 2004; Carroll et al. 2005), age (Anker et al. 2012a), hormonal influences (Larson et al. 2007), sweet intake (Perry et al. 2006; Holtz and Carroll 2011), and impulsivity (Anker et al. 2009), few studies have examined how behavioral or pharmacological treatments affect this maladaptive behavior, particularly in rats with individual differences (e.g., age) in vulnerability to drug abuse. Goals of the present study were to examine physical exercise as a behavioral treatment for the escalation of cocaine self-administration during LgA to the drug and to study possible individual differences in the effects of exercise in adolescent and adult female rats. Previous work indicates that a history of exercise decreases the escalation of cocaine intake (Smith et al. 2011), and the present study extends those findings to concurrent wheel and cocaine access in adolescent vs. adult rats that differ in drug abuse vulnerability during other phases of the addiction process (Anker and Carroll 2010; Schramm-Sapota et al. 2009; Spear 2000a, b, 2009, 2011).

A between- and within-group design was used, whereby adolescent and adult groups were randomly assigned access to either a locked or unlocked running wheel concurrently with cocaine self-administration for 16 days, after which the wheel access condition was reversed [i.e., locked running wheels became unlocked (LU) and vice versa (UL)] for an additional 10 days.

Materials and methods

Animals

A total of 60 female Wistar rats served as subjects in this study. Twenty-seven adult rats were obtained from Harlan Sprague-Dawley, Inc. (Madison, WI, USA) and began testing around postnatal day (PND) 90. The 33 adolescent rats were bred in our laboratory at the University of Minnesota from parents obtained from Harlan Sprague-Dawley, Inc. and began testing on PND 23. Adolescence in rats has been defined as PND 21–60 (Ojeda et al. 1980; Spear 2000a, b). Due to the difficulty of ushering subjects through the lengthy self-administration procedure, adolescent rats finished the study by the average age of PND 75. However, when adolescent rats that finished around PND 75 were compared to those that finished around PND 60, no differences were found in their behavioral data. Thus, they were included in the adolescent groups.

Females were used in this experiment as they readily acquire wheel running (Jones et al. 1990), and they run more than males (Boakes et al. 1999; Cosgrove et al. 2002; Eikelboom and Mills 1988; Lambert and Kinsley 1993), allowing a higher running baseline that might yield decreases in cocaine self-administration. Females are also more sensitive than males to the attenuating effects of wheel running on cocaine self-administration (Cosgrove et al. 2002). Estrous cycle was not monitored in adults, as animals were housed in their operant conditioning chambers during the experiment, and vaginal lavage could have disrupted the cycle as well as cocaine- and wheel-reinforced behavior. Additionally, randomly varying cycles allow results to be generalized across all phases of the estrous cycle.

After arrival at the laboratory, adult rats were pair-housed in plastic cages and allowed 3–10 days to acclimate before testing. Adults and adolescents had free access to laboratory chow (Teklad 2018, Harlan Laboratories, Madison, WI, USA) and water during this time. Upon commencement of behavioral testing, all rats were removed from the plastic cages and placed in individual operant conditioning chambers where they remained for the duration of the study. While in the chambers, rats continued to have free access to water, and adults were fed 16 g of ground food (LabDiet 5001, Purina Laboratory Chow, Minneapolis, MN, USA) approximately 15 min after their daily sessions at 3:15 p.m. to maintain them at 85 % of their free-feeding body weight. To allow for normal development, adolescents were initially fed ad libitum after session until they began consuming 16 g/day; thereafter, they were restricted to a 16 g/day allotment. All adolescents were restricted to the 16 g/day allotment by the time of catheter surgery. All rodent holding rooms were maintained at 24 °C and at 40–50 % humidity under a light/dark cycle of 12/12 h with room lights on at 6:00 a.m. The experimental protocol (1007A85632) was approved by the University of Minnesota Institutional Animal Care and Use Committee. The experiment was conducted in compliance with the Principles of Laboratory Animal Care (National Research Council 2003), and all laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care.

Apparatus

Animals were housed and tested in custom-built, octagonally shaped operant conditioning chambers with an attached running wheel as previously described (Zlebnik et al. 2010).

When lifted, a guillotine-style door allowed access to a freespinning 35.6-cm diameter running wheel (ENV-046, Med Associates Inc., St. Albans, VT, USA) that was fitted on the left side of each operant conditioning chamber. A rolling microswitch recorded quarter-wheel turns, and a mechanical lock could be put in place to allow entry but prevent rotation. Rats that entered the locked wheel did not tend to ambulate within the wheel, and the horizontal bars that comprised the wheel surface were not conducive to climbing (smooth and closely-spaced). Therefore, it was assumed that there was limited physical activity within the locked wheel.

During self-administration sessions, responding on the active/drug-paired lever activated the syringe pump (PHM-100, MedAssociates, Inc.) to deliver cocaine infusions through a swivel-tether (375/22PS, Instech, Plymouth Meeting, PA, USA; C313CS-MN, PlasticsOne, Roanoke, VA, USA) infusion system attached to an infusion harness (CIH95AB, Instech) worn by the rat. The swivel and tether allowed free movement within the operant chamber and easy access to the adjoining running wheel to accommodate concurrent drug self-administration and wheel running. Data collection and programming were conducted using PC computers with a Med-PC interface (MedAssociates, Inc.).

Drugs

Cocaine HCl (National Institute of Drug Abuse, Research Triangle Institute, Research Triangle Park, NC, USA) was dissolved in 0.9 % NaCl at a concentration of 1.6 mg cocaine HCl/1 ml saline, and heparin (5 USP/ml) was added to the cocaine solution to prevent catheter occlusion from thrombin accumulation. The flow rate of each cocaine infusion was 0.025 ml/s, and the duration of pump activation (1 s/100 g of body weight) was adjusted daily to provide a 0.4-mg/kg cocaine dose throughout self-administration testing. The 0.4-mg/kg cocaine dose was selected because it is within the limited range of doses that will elicit escalation of intake during LgA in the time frame of our investigation (Ahmed and Koob 1999; Anker et al. 2010; Carroll et al. 2011), and it is well accepted by both adults and adolescents (Anker and Carroll 2010; Carroll et al. 2011).

Catheterization surgery

One to three days after achieving wheel-running behavior, rats were surgically implanted with an indwelling catheter in the right jugular vein following the procedure previously described (Carroll and Boe 1982; Zlebnik et al. 2010). Following the surgical procedure, doors to the wheels remained closed, and rats were allowed a 3-day recovery period during which antibiotic (enrofloxacin, 10 mg/kg, sc) and analgesic (buprenorphine, 0.05 mg/kg, sc) medications were administered. Each rat was fitted with an infusion harness and tether that remained in place throughout the remainder of the study. After the recovery period, catheters were flushed with a solution (0.3 ml, iv) of heparinized saline (20 USP/ml) and cefazolin (10.0 mg/ml) at 3:00 p.m. daily to prevent catheter blockage and infection. Body weights were recorded daily at 8:00 a.m., and catheter patency was checked weekly at 3:00 p.m. by injecting a 0.1-ml solution containing ketamine (60 mg/kg), midazolam (3 mg/kg), and saline (KMS). If a loss of the righting reflex did not result from a KMS iv infusion, a second catheter was implanted in the left jugular vein, and the experiment was resumed in 3 days.

Procedure

Wheel training—The experimental procedure consisted of four phases: wheel training, surgery, self-administration training, and escalation. In the wheel training phase, rats were fitted with the infusion harness and tether in order to facilitate acclimation to the running wheel when connected to the harness/infusion system. Rats were first restricted to the wheel for a single 6-h session (9:00 a.m. to 3:00 p.m.) to expedite familiarization with the running wheel; then for the next 2 days, they had free access to the wheel from the operant

conditioning chamber during the daily 6-h sessions. During training, the house light was illuminated at the start of session, and the door to the wheel was opened. Response levers were present during wheel training; but they remained inactive, and responses were not recorded. Acquisition of wheel running was defined as a minimum of 100 full revolutions per 6-h session for three consecutive sessions. Most animals reached this criterion within the first three sessions. If an animal failed to reach this criterion within 1 week, it was excluded from the study.

Cocaine self-administration training—Following recovery from surgery, the door leading to the wheel remained closed, and rats were trained to lever press for iv infusions of cocaine (0.4 mg/kg) under a fixed-ratio 1 (FR 1) schedule of reinforcement during the daily 6-h sessions (9:00 a.m. to 3:00 p.m.). Sessions began with illumination of the house light, and during sessions, a response on the active/drug-paired lever started the infusion pump and illuminated the stimulus lights located directly above the lever for the duration of the infusion. Responses on the active lever during the length of the infusion (2–3 s for adults and 1–3 s for adolescents) were recorded but had no programmed consequences. Responses on the inactive/activity lever illuminated the stimulus lights above that lever for the same duration as an infusion but did not activate the infusion pump. Initially, three experimenter-delivered priming infusions of 0.4 mg/kg cocaine were administered periodically during each training session (9:00 a.m., 11:00 a.m., and 1:00 p.m.) followed by a placement of a small amount of ground food on the active/drug-paired lever. Acquisition was complete when rats earned 40 infusions during a single session in the absence of experimenter-delivered primes.

Escalation: conditions 1 and 2—Once rats achieved acquisition of cocaine self-administration, they were allowed to self-administer unlimited infusions during daily 6-h sessions. The door leading to the wheel from the operant conditioning chamber was opened at the start of session (9:00 a.m.), and rats had free access to both cocaine self-administration and wheel running for the remainder of the session. To serve as a control condition for wheel running, half of the rats had their running wheels locked with a mechanical brake, which allowed them to enter the wheel but not to turn it. The escalation period was divided into two conditions: condition 1 lasted for 16 days in order to facilitate escalation of cocaine intake, and condition 2 lasted for only 10 days in order to accommodate the short period of adolescence (PND 23–60). During condition 1, half of the adults (Adult UL) and half of the adolescents (Adol UL) had access to an unlocked running wheel during cocaine self-administration sessions, while the remainder of the adults (Adult LU) and adolescents (Adol LU) had concurrent access to a locked running wheel. During condition 2, to evaluate within-group changes in wheel access conditions on cocaine self-administration, running wheels were locked for the animals that had unlocked running wheels during condition 1 (Adult UL and Adol UL) and were unlocked for the animals that had locked running wheels during condition 1 (Adult LU and Adol LU). Escalation was defined as a significantly greater number of infusions during the last 2 days compared to the first 2 days of each condition.

Data analysis

Active and inactive lever responses, responses during infusions (RDI; adjusted for infusion length), cocaine infusions, and wheel revolutions were averaged into blocks of either 8 days (condition 1) or 5 days (condition 2) each and analyzed using two-factor repeated-measures ANOVA (group $\times$ block). Escalation of cocaine intake was assessed by comparing the average of the first and last 2 days of each condition. Hourly infusions were averaged for days 1, 8, 16, and 24 and analyzed using two-factor repeated-measures ANOVA to assess changes in hourly intake at specific, regular time points over the course of the experiment.

After significant main effects and interactions were found, post hoc tests were performed with Fisher's LSD protected *t* tests using GB Stat (Dynamic Microsystems, Inc., Silver Spring, MD, USA). Pearson's product-moment correlations with R (R Package 2.13.1, R-project.org) were used to determine whether mean wheel revolutions during periods of wheel access were correlated with cocaine infusions earned during these periods and also during periods when unlocked wheel access was not available.

Results

Mean body weights did not differ among the two adolescent groups or among the two adult groups across any of the experimental phases. Figure 1 illustrates the mean number of cocaine (0.4 mg/kg) infusions self-administered under the FR 1 schedule during condition 1 (days 1–16) and condition 2 (days 17–26). Comparison of the adolescent groups indicated no significant main effects of group or session block, but there was a significant interaction ($F_{1,131}=17.87$, $p<0.0001$). Post hoc tests revealed that Adol LU rats self-administered significantly more cocaine than Adol UL rats over condition 1 (days 1–8, 9–16 $p<0.01$, Fig. 1a). When wheel access was introduced during condition 2, Adol LU rats reversed their level of intake and self-administered significantly fewer infusions (days 9–16 vs. days 17–21, $p<0.01$) despite having reached a high level of intake during condition 1. Cocaine intake increased notably for Adol UL rats when unlocked wheel access was suspended during condition 2 (days 9–16 vs. days 17–21, $p<0.01$), and Adol UL rats administered significantly more infusions than Adol LU rats during this condition (days 17–21, $p<0.01$; days 22–26, $p<0.05$).

To assess escalation of cocaine intake, the mean of the first 2 days was compared to the mean of the last 2 days of each condition. Post hoc tests following significant main effects of group ($F_{1,65}=14.27$, $p=0.0007$) and session block ($F_{1,65}=13.49$, $p=0.0009$) and a significant interaction ($F_{1,65}=4.60$, $p=0.04$) indicated Adol LU rats escalated their intake over condition 1 (days 1–2 vs. 15–16, $p<0.01$, Fig. 1a), but concurrent access to a running wheel during this condition prevented escalated intake in the Adol UL rats. In condition 2, there was a main effect of group ($F_{1,43}=4.43$, $p=0.0481$) but no effect of session block or interaction.

In contrast to the results for adolescents, Fig. 1b shows that neither of the adult groups escalated their intake, and no significant differences emerged when comparing infusions earned over the 26-day period between Adult UL and Adult LU rats, indicating that wheel access did little to attenuate cocaine intake in adults. While Adult LU and Adol LU rats did not differ in infusions over conditions 1 and 2 (Fig. 1d), a significant main effect of session block ($F_{3,123}=8.33$, $p<0.0001$) and a significant interaction ($F_{3,123}=5.378$; $p=0.0012$) was found when comparing Adult UL and Adol UL rats. Adult UL rats earned more infusions than Adol UL rats at the start of condition 1 (days 1–8, $p<0.05$, Fig. 1c), but their intake was similar by the end of this condition (days 9–16, Fig. 1c). When unlocked wheel access was suspended for these groups in condition 2, Adol UL rats increased their cocaine intake (days 9–16 vs. days 17–21, $p<0.01$) while Adult UL rats did not. Overall in conditions 1 and 2, cocaine intake for adolescents was significantly more responsive to change in wheel access than cocaine intake for adults.

Hourly cocaine intake for days 1, 8, 16 (condition 1), and 24 (condition 2) is depicted in Fig. 2. These days were selected as they sample hourly intake at regularly spaced intervals in the experiment, and they clearly and accurately show changes in rate of intake over time. There was no effect of hour within session for any group. However, when comparing the means of these days for the adolescent groups, results of the ANOVA indicated no main effect of group but a significant effect of session block ($F_{3,119}=5.95$, $p=0.001$) and a significant

interaction ($F_{3,119}=19.50$, $p<0.0001$). Similar to mean daily infusions in Fig. 1a, the mean hourly intake or rate of intake for Adol LU rats increased significantly by the end of condition 1 when they had locked wheel access (day 1 vs. day 16, $p<0.01$, Fig. 2a) but decreased significantly with the introduction of unlocked wheel access during condition 2 (day 16 vs. day 24, $p<0.01$). The increase in the rate of intake over condition 1 was absent in the Adol UL group, and Adol UL rats had a lower rate of intake than the Adol LU rats on days 1 and 16 (day 1, $p<0.05$; day 16, $p<0.01$). When unlocked wheel access was terminated for the Adol UL rats in condition 2, the amount of drug consumed per hour significantly increased for this group, making their rate of intake on day 24 greater than on day 16 ($p<0.01$) and significantly higher than that of Adol LU rats on day 24 ($p<0.01$). Therefore, for Adol UL rats, unlocked wheel access during condition 1 prevented the increase in hourly rate of cocaine intake seen with Adol LU rats, and the reversal of wheel access conditions in condition 2 resulted in the reversal of within-group intake patterns, where Adol UL rats increased their intake rate while Adol LU rats decreased theirs.

Opposite to the differences seen among the adolescent groups, Adult UL and Adult LU rats had comparable rates of intake over both conditions 1 and 2 (Fig. 2b). However, when comparing Adult LU and Adol LU rats (Fig. 2d), there was a significant main effect of session block ($F_{3,95}=6.25$, $p=0.0008$) and a significant group $\times$ block interaction ($F_{3,95}=7.50$, $p=0.0002$). The rate of within-session cocaine intake over condition 1 for Adult LU and Adol LU rats was similar, but once unlocked wheel access was introduced in condition 2, Adol LU rats significantly decreased their rate of intake compared to that in condition 1 ($p<0.01$) and compared to Adult LU rats ($p<0.01$) that did not alter their rate of intake. In contrast, following a significant effect of session block ($F_{3,111}=6.15$, $p=0.0008$) and a significant group $\times$ block interaction ($F_{3,111}=2.87$, $p=0.0415$), post hoc analyses showed that Adol UL and Adult UL rats differed in their rate of intake only on day 1 ($p<0.05$), where Adult UL rats consumed more drug per hour than Adol UL rats (Fig. 2c). By day 8, Adol UL and Adult UL rats consumed similar amounts of drug per hour, and this persisted throughout condition 1 and into condition 2 with the introduction of the unlocked wheel. Taken as a whole, the analysis of hourly rate of cocaine intake indicated that presence or absence of the unlocked running wheel markedly affected the rate of intake in adolescent but not adult rats.

Since an FR 1 schedule was used, the number of responses on the active/drug-paired lever (results not shown) was very similar to the number of infusions earned. Responses during the duration of the infusion (see “Methods”) also were recorded but did not result in additional infusions. This type of ineffective responding (i.e., RDI) could indicate impairment in behavioral inhibition and may be considered a measure of impulsivity of action associated with chronic psychostimulant use (Perry and Carroll 2008; Anker et al. 2011; Anker et al. 2012a; Carroll et al. 2012). When comparing the adolescent groups, there was no significant effect of group, but there was a significant effect of session block ($F_{3,123}=4.41$, $p=0.0062$) and a significant group $\times$ session block interaction ($F_{3,123}=7.54$, $p=0.0002$). Neither the Adol LU nor the Adol UL rats significantly increased their RDI over condition 1 (Table 1). However, consistent with their pattern of cocaine intake, Adol LU rats made significantly more RDI than Adol UL rats during the second half of condition 1 (days 9–16, $p<0.05$). With the change in wheel access conditions in condition 2, Adol LU rats decreased their RDI (days 9–16 vs. days 17–21, $p<0.01$), while Adol UL rats increased theirs (days 9–16 vs. days 17–21, $p<0.05$). Together, these results suggest that RDI increases as cocaine intake increases and, like cocaine intake, can be reduced with exposure to an unlocked running wheel in adolescents.

Comparison of RDI for Adult LU and UL rats resulted in a significant effect of session block ($F_{3,107}=4.88$, $p=0.0037$) but no main effect of group and no significant interaction.

Also, there was no interaction in the analysis comparing the Adol LU rats and Adult LU rats, even though there were main effects of group ($F_{1,111}=5.45$, $p=0.0275$) and session block ($F_{3,111}=6.48$, $p=0.0006$). However, following no main effects, there was a significant group $\times$ session block interaction ($F_{3,119}=9.11$, $p<0.0001$) comparing the Adol UL and Adult UL rats. An interesting trend emerged: Adult UL rats (vs. Adol UL rats) made significantly more RDI by the end of condition 1 ($p<0.01$); however, when wheel access was suspended in condition 2, Adult UL rats significantly reduced their RDI (days 9–16 vs. days 17–21, $p<0.01$), while Adol UL significantly increased theirs (days 9–16 vs. days 17–21, $p<0.01$), indicating that RDI for adolescents was potentiated by removing unlocked wheel access.

Responding on the inactive or control lever was analyzed as a measure of general activity. During condition 1, there were significant main effects of group ($F_{1,123}=7.99$, $p=0.0084$) and session block ($F_{3,123}=8.54$, $p<0.0001$) but no significant interaction when comparing inactive lever responses between Adol UL and Adol LU rats (Table 1). For the Adult UL and Adol UL rats, there was a significant effect of group ($F_{1,123}=5.94$, $p=0.021$) and a significant group $\times$ session block interaction ($F_{3,123}=8.82$, $p<0.0001$). Adol UL rats had significantly higher inactive lever responding during the first half of condition 1 compared to the rest of condition 1 and condition 2 (days 1–8 vs. days 9–16, 17–21, and 22–26; $p<0.01$), and Adol UL rats also responded on the inactive lever more than Adult UL rats throughout condition 1 ($p<0.01$). There were no differences in inactive responding between either Adol LU and Adult LU rats or Adult UL and Adult LU rats. Thus, differences in cocaine intake among the groups were likely due to differences in drug seeking and not differences in general activity as measured by responding on the inactive lever.

Figure 3 shows mean daily wheel revolutions over condition 1 for Adol UL and Adult UL rats and over condition 2 for Adol LU and Adult LU rats. The pattern of daily wheel revolutions was analyzed for group differences and differences due to prior cocaine exposure. In contrast to the number of cocaine infusions earned, there were no significant differences between Adol UL and Adult UL rats in the mean number of revolutions achieved during condition 1. Further, there were no age differences in wheel revolutions throughout condition 2 when comparing Adol LU and Adult LU rats. However, in contrast to rats with wheel access during condition 1, rats with wheel access during condition 2 (Adol LU and Adult LU) escalated their wheel revolutions over that 10-day period (days 17–18 vs. days 25–26, $F_{1,43}=4.50$, $p=0.0465$). There were no differences in mean hourly revolutions among or within any of the groups.

In order to characterize the relationship between wheel running and cocaine intake, mean wheel revolutions and cocaine infusions were correlated for each group (Fig. 4). During periods of unlocked wheel access, all groups demonstrated a pattern of cocaine intake that was negatively correlated with the number of wheel revolutions. During condition 1, a statistically significant negative correlation was found between revolutions and infusions for both Adol UL ($r^2=0.46$, $p=0.0018$, Fig. 4a) and Adult UL ($r^2=0.69$, $p<0.0001$, Fig. 4c) rats, and similar significant negative correlations were calculated for Adol LU ($r^2=0.69$, $p=0.0014$, Fig. 4b) and Adult LU ($r^2=0.48$, $p=0.014$, Fig. 4d) rats during condition 2. Thus, consistently throughout the conditions when an unlocked wheel was available, the number of revolutions and cocaine infusions were inversely and significantly related.

Mean wheel revolutions during periods of unlocked wheel access were correlated with mean cocaine infusions during periods with locked wheel access to examine whether innate differences in activity seeking were related to drug seeking. No significant correlations were found between wheel revolutions during condition 1 and cocaine infusions during condition

2 for Adol UL and Adult UL rats and also between cocaine infusions during condition 1 and wheel revolutions during condition 2 for Adol LU and Adult LU rats (data not shown).

Discussion

The principal finding of this study is that concurrent access to exercise (wheel running) decreased cocaine intake in adolescent but not adult female rats under LgA conditions. Concurrent unlocked wheel access not only decreased cocaine intake in adolescent rats but also prevented the escalation of intake. Further, access to an unlocked wheel reduced cocaine self-administration even when wheel access began after a period of escalated intake (LU). However, concurrent access was determined to be necessary in this model, as removing availability of the unlocked wheel after 16 days of access (UL) caused the adolescents to initiate higher levels of intake. In contrast to the results with adolescents, unlocked wheel access had little effect on cocaine intake in adult female rats.

Initial findings with animal models and individual differences in treatment effects indicate that female rats (Campbell et al. 2002; Carroll et al. 2001b) and monkeys (Cosgrove and Carroll 2004) show more drug seeking behavior than males, and females have a better response than males to pharmacological treatments and behavioral interventions such as environmental enrichment with preferred dietary substances (Campbell and Carroll 2000) or concurrent access to exercise (Cosgrove et al. 2002). However, no sex differences were found in reduced escalation of cocaine intake due to a history of wheel running in female vs. male rats (Smith et al. 2011). Treatment outcomes may vary with respect to the specific individual difference under examination and the treatment methods used. For example, in contrast to the studies showing that females had a greater response to pharmacological treatments for drug-seeking behavior than males (see above), recent studies comparing other individual differences indicate that addiction-resistant, low-saccharin-preferring rats (LoS) are more responsive to pharmacological treatments such as baclofen (Holtz and Carroll 2011) and progesterone (Anker et al. 2012b) than addiction-prone, high saccharin-preferring (HiS) rats.

The results of the present study build on previous work demonstrating greater drug seeking and drug taking in adolescents than adults. While in some studies no age differences were found (Belluzzi et al. 2005; Frantz et al. 2007; Kantak et al. 2007; Kerstetter and Kantak 2007; Leslie et al. 2004), others showed that adolescents (vs. adults) consumed more drug (Anker and Carroll 2010; Anker et al. 2012a; Fullgrabe et al. 2007; Chen et al. 2007; Levin et al. 2007, 2003; Shahbazi et al. 2008; Vetter et al. 2007) and demonstrated greater sensitivity to drugs with several measures including conditioned place preference (Badanich et al. 2006; Brenhouse and Anderson 2008; Brenhouse et al. 2008; Zakharova et al. 2009) and drug-induced locomotor activity (Parylak et al. 2008; Catlow and Kirstein 2005; Snyder et al. 1998). Animal models of the human drug abuse process also identify adolescents as more vulnerable than adults during critical phases of addiction, such as acquisition (Perry et al. 2007), extinction (Anker and Carroll 2010), and reinstatement (Anker and Carroll 2010). In a recent study in our laboratory, greater escalation of methamphetamine self-administration was found in adolescent vs. adult male rats (Anker et al. 2012a), and this was in agreement with the present findings that showed escalated cocaine intake in adolescents (Adol LU), but not adults (Adult LU), that had locked wheel access during condition 1. Escalation of intake was expected in the Adult LU rats during the 16 days of condition 1, as previous work from our lab has demonstrated escalation in adult females in as little as 10 days under the same access and dose conditions (Zlebnik et al. 2010). However, most studies do not report escalation of intake until the third week of 6-h access (Anker et al. 2010; Carroll et al. 2011; Anker et al. 2012b); thus, for adolescents to escalate their cocaine

intake in only 16 days while adults did not highlights adolescents' greater susceptibility to addiction.

Although others have examined age differences in drug self-administration and drug sensitivity, little work has been done to compare treatment effects in adolescents and adults. Some groups have looked at the effect of adolescent wheel exposure on subsequent drug seeking and taking during adulthood (Smith et al. 2008, 2011, 2012; Smith and Pitts 2011; Thanos et al. 2010), but the present study was the first to directly compare wheel running as a deterrent to drug taking in both adolescents and adults. The results indicating that adolescents are more responsive to exercise as a treatment than adults are important given the relative vulnerability of adolescents (vs. adults) to addiction (Doremus-Fitzwater et al. 2010; Spear 2009; but see Schramm-Sapota et al. 2011; Kerstetter and Kantak 2007), and they agree with previous work showing greater treatment success in drug-prone females (vs. males) (Campbell et al. 2002; Carroll et al. 2001a, b; Cosgrove et al. 2002). Furthermore, exercise may be advantageous over the use of pharmaceutical interventions in adolescents who are still undergoing critical development (Koelch et al. 2008; McVoy and Findling 2009).

While the current findings did not show wheel running as an effective intervention in adults, prior work by others indicates that separate and long-term (6 weeks) exposure to exercise in rats that were initially exposed during early adolescence reduced the escalation of cocaine intake in both male and female adults (Smith et al. 2011). Chronic access to a running wheel that is available at a different time than drug self-administration (e.g., Lynch et al. 2010; Smith et al. 2008, 2011, 2012; Smith and Pitts 2011; Thanos et al. 2010) vs. limited concurrent access to wheel running and drug self-administration (e.g., Cosgrove et al. 2002; Miller et al. 2012) are different methods of exercise exposure that may rely on different mechanisms of action to alter drug seeking. Previous work comparing sequential vs. concurrent access to a preferred dietary substance revealed a more robust reduction in drug intake with concurrent access compared with sequential access (Campbell and Carroll 2000). However, concurrent and sequential methods of providing wheel access have not been compared directly within a study using similar procedures and controlling for age during exposure. Further work is needed to identify the optimal conditions for providing opportunities for exercise as a strategy to reduce drug abuse, but it is promising that both the sequential and concurrent procedures have shown robust decreases in drug self-administration, indicating that exercise is a highly efficacious method of reducing drug-reinforced behavior.

In addition to impacting drug intake, the present results suggest that wheel running reduced a possible form of impulsive behavior that is related to relapse (Perry et al. 2006). Adol LU rats took more drug than Adol UL rats during the latter part of condition 1 and made more responses during infusions as well. Responding during infusions decreased with the introduction of unlocked wheel access in condition 2, and opposite results were seen for Adol UL rats with the removal of wheel access. These results suggest that RDI may be related to heightened drug intake and are sensitive to the presence or absence of unlocked wheel exposure. Support for these findings comes from a recent study in our laboratory that measured greater responses during infusions for adolescents (vs. adults) during the escalation of methamphetamine self-administration (Anker et al. 2012a). Other work has demonstrated more responding from adolescents during periods of signaled time-outs during cocaine (Anker et al. 2011) and amphetamine (Shabahzi et al. 2008) self-administration. As mentioned, RDI could be an indication of impaired behavioral inhibition like the type of perseverative responding that is characteristic of the stop-signal reaction time task or the go/no-go task (Dalley et al. 2011). Alternatively, this type of responding could be premature responding for the next infusion, which would make it similar to performance on the five-

choice serial reaction time task. Regardless, RDI appears to be related to impulsive and/or compulsive action and can be modulated by factors that affect impulsivity and drug seeking. For instance, Cummins and Leri (2008) found that RDI for animals self-administering sucrose increased with food deprivation, indicating that responding during administration of a reinforcer is sensitive to changes in motivation for reward. Impulsivity (Carroll et al. 2009) and drug seeking (Comer et al. 1995a; Comer et al. 1995b) are also enhanced by food restriction. Therefore, it is noteworthy that wheel running may decrease behaviors associated with vulnerability to (e.g., impulsivity) and the development of (e.g., compulsivity) addiction (Dalley et al. 2011; de Wit 2009).

Unlike the differences seen with cocaine intake, no differences were detected in the number of wheel revolutions between adolescent and adult rats. This is surprising, given age-related differences in activity levels and evidence of greater cocaine-induced locomotion in adolescents (Parylak et al. 2008; Snyder et al. 1998; Badanich et al. 2008; Caster et al. 2007; Catlow and Kirstein 2005). However, our comparison of revolutions does not take into account that adolescents likely made many more steps to complete a revolution, as their stride length is roughly half that of an adult. Given this and the differences in body weight and muscle mass between adolescents and adults, it is difficult to analyze effort as a function of age. Nevertheless, in the adolescent groups, the added effort required for running makes the choice of wheel running over cocaine self-administration even more compelling. There are also other reports of no age differences in cocaine-induced locomotion (Adriani et al. 1998; Camarini et al. 2008) and reports of more locomotion in adults under certain conditions (Laviola et al. 1995; Zombeck et al. 2009, 2010; Spear and Brake 1983). Adolescents displayed greater general activity (as measured by inactive/activity lever responding) in the present study, but this result was specific to the Adol UL group during unlocked wheel access in condition 1. Since the adolescent groups did not differ in inactive/activity lever responses throughout the testing period, and the elevated responding for Adol UL (vs. Adult UL) rats occurred only during wheel access, perhaps early cocaine exposure interacted with wheel running to produce greater undirected arousal that decreased or became more directed with additional exposure to cocaine.

Another interesting finding of this experiment, however, is that both Adol LU and Adult LU rats escalated their wheel running over a short period (10 days) of unlocked wheel access (condition 2) after chronic exposure to cocaine (condition 1). This was in contrast to the Adol UL and Adult UL rats that did not escalate their running during early cocaine exposure during condition 1 (16 days). Since previous work in our lab has shown that wheel running in the absence of cocaine self-administration escalated over a 21-day period (Larson and Carroll 2005), it is possible that concurrent cocaine intake augmented wheel running in the present study, resulting in escalation of running over a much shorter period of 10 days. However, this is unlikely, given that the Adol UL and Adult UL rats did not display potentiated running with concurrent cocaine self-administration during condition 1. Further, others showed decreases in wheel running when cocaine (Cosgrove et al. 2002) and methamphetamine (Miller et al. 2012) were concurrently available during short-access periods (5 h/day for 5 days and 1 h/day for 14 days, respectively). In the present study, we used longer periods of cocaine access (6 h/day for 26 days), resulting in much more cocaine intake and escalation of intake in one group (Adol LU rats during 16 days of condition 1). Therefore, it is possible that the escalation of wheel running for Adol and Adult LU rats during condition 2 was compensatory and indicative of the reward allostasis or change in reward set point that accompanies chronic drug use (Ahmed and Koob 1998, 1999, 2005; Koob and Le Moal 2001). Results such as these may suggest a greater role for exercise in the treatment of drug bingeing in addition to other critical phases of the human drug abuse process.

If the effects of both cocaine and exercise can contribute to achieving the reward threshold, then an investigation of their interaction is warranted. Although a rigorous behavioral economics analysis was not undertaken, it may be concluded from the data that wheel running and cocaine self-administration at the 0.4 mg/kg dose are substitutable based on the strength of the correlations relating these behaviors. Further, the demand for cocaine may be more elastic in adolescents than adults because the presence or absence of the unlocked running wheel had a greater effect on cocaine intake in adolescents (Green and Freed 1993). A thorough economic analysis using several doses of cocaine and wheel access durations should be performed in order to make additional conclusions regarding the nature of the interaction between the two alternative reinforcers.

The results of the present study corroborate findings that indicate that exercise may be a useful treatment intervention for drug abuse in humans. Laboratory studies in humans (Vuchinich and Tucker 1983; Carroll 1996) and animals (Campbell and Carroll 2000; Griffiths et al. 1980) indicated that drug intake was reduced in the presence of alternative reinforcement, and correlational analyses showed reliable inverse relationships between alternative reinforcement and negative consequences of drug abuse in alcoholics (Vuchinich and Tucker 1996) and cocaine abusers (Van Etten et al. 1998). In adolescents, alternative reinforcement in the form of exercise was associated with improvement in risk factors (e.g., low self-esteem, depression, lack of self control) for substance use (Collingwood et al. 2000), and lower alcohol, cigarette, and marijuana use (Terry-McElrath et al. 2011). Further, several studies noted significantly lower substance use frequency during adolescence (Terry-McElrath and O'Malley 2011) and throughout early adulthood (Charilaou et al. 2009; Korhonen et al. 2009) in people who engaged in sports, athletics, or exercise during adolescence, with the greatest effect occurring in those who engaged in endurance sports such as running (Wichstrom and Wichstrom 2009). Furthermore, in adults, moderate-intensity aerobic exercise decreased cravings for alcohol (Ussher et al. 2004), cigarettes (Daniel et al. 2004), and cannabis (Buchowski et al. 2011), while brief episodes of isometric (Ussher et al. 2006, 2009) and aerobic (Ussher et al. 2001; Daniel et al. 2004; Williams et al. 2011) exercise also alleviated symptoms of tobacco withdrawal. Therefore, results from the human literature are consistent with those of the present study and support a role for exercise as a drug treatment approach.

In summary, this study used both between- and within-subjects comparisons to investigate the effects of concurrent exercise on cocaine self-administration under LgA conditions in adolescent and adult female rats, which differ in drug abuse vulnerability. Between-subjects comparisons indicated that concurrent access to exercise decreased cocaine intake in adolescents but not adults, while within-subjects comparisons proved concurrent wheel access to be necessary to suppress cocaine intake in adolescents. Although previous reports supported a role for wheel running in decreasing drug-seeking behaviors, this investigation was the first to thoroughly examine age and individual differences in the efficacy of exercise as a behavioral treatment for escalation, a critical component of the addiction process. Thus, the present findings suggest a role for exercise as a behavioral treatment intervention during critical transition phases of the addiction process in individuals with drug abuse vulnerability.

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Fig. 1.

Mean (±SEM) cocaine (0.4 mg/kg) infusions self-administered over conditions 1 and 2. **a** Adol LU rats earned significantly more infusions than Adol UL rats over condition 1 (days 1–8, 9–16; ** indicate $p < 0.01$) and also escalated their cocaine intake over this period (days 1–2 vs. 15–16, @ indicates $p < 0.01$). With reversal of wheel access at the onset of condition 2, Adol LU rats decreased, while Adol UL rats increased, cocaine intake (days 9–16 vs. days 17–21, # indicates $p < 0.01$); and Adol UL rats administered significantly more infusions than Adol LU rats throughout condition 2 (days 17–21, ** indicate $p < 0.01$; days 22–26, * indicates $p < 0.05$). **b** There were no significant differences in cocaine intake between Adult UL and Adult LU rats. **c** Adult UL rats initially administered more cocaine infusions than Adol UL rats during condition 1 (days 1–8, * indicates $p < 0.05$), but both groups administered similar amounts by the end of the condition. Removing unlocked wheel access in condition 2 was met with an increase in cocaine infusions earned by Adol UL but not Adult UL rats (days 17–21, ** indicate $p < 0.01$). **d** There were no significant differences in cocaine intake between Adol LU and Adult LU rats.

Fig. 2.

Mean (±SEM) hourly cocaine (0.4 mg/kg) infusions self-administered over days 1, 8, 16 (condition 1), and 24 (condition 2). **a** Adol LU rats maintained a higher rate of cocaine intake than Adol UL rats over condition 1 (day1, * indicates $p < 0.05$; day 16, ** indicate $p < 0.01$) and escalated their rate of intake over this condition (day 1 vs. day 16, (x00040) indicates $p < 0.01$). With the reversal of wheel access during condition 2, Adol LU rats decreased, while Adol UL rats increased, their rate of cocaine intake (day 16 vs. day 24, # indicates $p < 0.01$), with Adol LU rats maintaining a significantly lower rate of intake than Adol UL rats on day 24 (** indicate $p < 0.01$). **b** There were no significant differences in rate of cocaine intake between the Adult UL and Adult LU rats. **c** While Adol UL rats significantly increased their rate of intake with the onset of locked wheel access during condition 2 (day 16 vs. day 24, # indicates $p < 0.01$), there was only a difference in rate of intake on day 1 between Adol UL and Adult UL rats (* indicates $p < 0.05$). **d** However, Adol LU rats significantly decreased rate of intake with the introduction of unlocked wheel access in condition 2 (day 16 vs. day 24, # indicates $p < 0.01$), while Adult LU rats were unresponsive to this change in wheel access and maintained a higher rate of intake than the Adol LU rats during this condition (** indicate $p < 0.01$)

Fig. 3.

Mean ($\pm$ SEM) wheel revolutions over conditions 1 and 2. There were no significant age differences in wheel revolutions during condition 1 and condition 2. However, Adol LU and Adult LU rats escalated their wheel revolutions during condition 2 with introduction of the unlocked wheel (days 17–18 vs. days 25–26, (x00040) indicates $p < 0.05$)

Fig. 4.

a–d Mean cocaine infusions correlated with mean wheel revolutions for each group. Each group demonstrated a negative linear relationship between cocaine infusions and wheel revolutions during sessions when both were concurrently available

Table 1
Mean (±SEM) active lever responses during infusions and inactive lever responses

Active lever responses during infusions					Inactive lever responses			
Condition 1		Condition 2			Condition 1		Condition 2	
Days	1-8	9-16	17-21	22-26	1-8	9-16	17-21	22-26
<i>Adol</i>								
UL	7.5 (1.6)ab	4.6 (1.3)b ^{*, ****}	9.0 (2.5)a ^{*, ****}	4.3 (1.1)b	46.0 (11.2)a ^{****}	24.4 (7.7)b ^{****}	16.8 (4.1)b	17.2 (5.3)b
LU	7.9 (1.6)a	9.1 (3.5)a [*]	0.63 (0.4)b ^{**}	2.1 (0.6)b	13.6 (4.7)	8.0 (1.9)	4.1 (1.3)	3.9 (1.1)
<i>Adult</i>								
UL	8.4 (1.7)a	12.0 (2.7)a ^{****}	1.1 (0.4)b ^{****}	10.0 (4.4)a	3.7 (0.9) ^{****}	3.7 (1.2) ^{****}	3.5 (2.1)	2.7 (0.9)
LU	11.3 (2.7)	14.6 (4.6)	7.7 (2.3)	6.56 (2.5)	9.6 (2.7)	10.8 (2.1)	11.2 (4.4)	12.0 (4.3)

Within-group differences are indicated by lowercase letter a vs. b at $p < 0.05$ (ab not different from either a or b)
Between-group differences are indicated for UL vs. LU and Adol vs. Adult

* $p < 0.05$ (UL vs. LU);
 ** $p < 0.01$ (UL vs. LU);
 *** $p < 0.05$ (Adol vs. Adult);
 **** $p < 0.01$ (Adol vs. Adult)