Published in final edited form as:

Drug Alcohol Depend. 2012 February 1; 121(1-2): 90–96. doi:10.1016/j.drugalcdep.2011.08.013.

Reciprocal inhibitory effects of intravenous d-methamphetamine self-administration and wheel activity in rats

ML Miller, BD Vaillancourt, MJ Wright Jr., SM Aarde, SA Vandewater, KM Creehan, and MA Taffe

Committee on the Neurobiology of Addictive Disorders; The Scripps Research Institute, La Jolla, CA, USA

Abstract

Background—Some epidemiological and cessation studies suggest physical exercise attenuates or prevents recreational drug use in humans. Preclinical studies indicate wheel activity reduces cocaine self-administration in rats; this may, however, require the establishment of compulsive wheel activity.

Methods—Effects of concurrent wheel activity on intravenous d-methamphetamine (METH) self-administration were examined in male Wistar and Sprague Dawley rats with negligible prior wheel experience. Wistar rats self-administered METH (0.05 mg/kg/inf) under a fixed-ratio 1 (FR1) schedule with concurrent access to an activity wheel during sessions 1–14, 8–21 or 15–21. Control rats which did not self-administer METH had access to an activity wheel during sessions 1–14, 8–21 or 15–28. Sprague Dawley rats self-administered METH (0.1 mg/kg/inf) under FR1 for 14 sessions with either concurrent access to a locked or an unlocked activity wheel.

Results—METH self-administration was lower when the wheel was available concurrently from the start of self-administration training in both strains, even though Sprague Dawley rats self-administered twice as many METH infusions and ran one-sixth as much on the wheel compared to Wistar rats. Wheel access initiated after 7 or 14 days had no effect on METH self-administration in Wistar rats. Wheel activity was significantly reduced in these groups compared with the group with concurrent wheel and METH access for the first 14 sessions.

Conclusions—These data show METH self-administration is reduced by exercise if initiated from the start of self-administration and that prior METH self-administration experience interferes with the value of exercise as a reinforcer.

Keywords

d-methamphetamine; self-administration; running; rats

© 2011 Elsevier Ireland Ltd. All rights reserved.

Address Correspondence to: Dr. Michael A. Taffe, Committee on the Neurobiology of Addictive Disorders, SP30-2400; 10550 North Torrey Pines Road; The Scripps Research Institute, La Jolla, CA 92037; USA; Phone: 1-858-784-7228; Fax: 858-784-7405; mtaffe@scripps.edu.

Contributors: MAT designed the study with significant input from MJW. KMC, BDV, and SAV collected and organized the data, and completed initial data analyses. MLM, BDV, and MJW conducted literature searches and provided summaries of previous related work. MAT and SMA undertook the statistical analysis; MAT and MLM drafted the manuscript with assistance from MJW and SMA on integration and analysis. All authors contributed to and have approved the final manuscript.

Conflict of Interest: No conflict declared.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Epidemiological evidence shows that human adolescents who are involved in sporting activities have a reduced risk for using drugs of abuse, including cigarettes, marijuana and cocaine (Taliaferro et al., 2010). Although efforts to determine if exercise has beneficial effects in smoking-cessation programs have been mixed (see (Ussher et al., 2008) for review) one of the largest randomized controlled trials found beneficial effects up to 12 months after treatment (Marcus et al., 1999). Additionally, habitual exercisers that meet diagnostic criteria for exercise *dependence* smoked less than non-dependent exercisers (Lejoyeux et al., 2008). Due to sociological and other factors determining exercise participation in humans, it is unclear whether there are neurobiological effects of exercise that influence substance use or dependence specifically. Thus, there exists a need for preclinical research studies on the behavioral and neurobiological mechanisms responsible for effects of physical activity on drug abuse to fully evaluate these new avenues to counter the establishment or continuation of substance use.

Many rodent species will run spontaneously when provided with an activity wheel (Sherwin, 1998). In addition, access to an activity wheel increases the probability of an operant response (Hundt and Premack, 1963; Premack et al., 1964) and will maintain lever pressing of rats under a variety of schedules (Belke, 2010; Belke and Hancock, 2003; Collier and Hirsch, 1971; Pierce et al., 1986). Although there are subtle differences in response patterning maintained by wheel activity compared to sucrose-maintained responding (i.e., longer post-reinforcement pauses and lower local rates of responding), there is ample evidence that wheel activity functions as a positive reinforcer (Belke, 2000, 2004, 2006). Similar to other reinforcers, the ability of wheel activity to serve as a reinforcer depends on magnitude (i.e., duration) and the concurrent availability of other reinforcers (Belke, 1997, 2000, 2006; Belke and Hancock, 2003). Disruptions in lever pressing due to pre-session injections of d-amphetamine or cocaine are similar in both wheel- and sucrose-maintained responding (Belke and Dunbar, 2001; Belke et al., 2005). In addition, Pavlovian procedures show that wheel-activity can produce a conditioned place preference (Belke et al., 2005), conditioned taste aversion (Forristall et al., 2007), and conditioned place avoidance (Masaki and Nakajima, 2008) depending on the temporal sequence of wheel/cue presentation. In aggregate the evidence shows that wheel activity can serve as a competing or substitute reward, which may thereby decrease drug seeking.

Initial evidence from rodent models supports this inference. Concurrent access to an activity wheel suppresses cocaine (Cosgrove et al., 2002), amphetamine (Kanarek et al., 1995) and ethanol (McMillan et al., 1995) self-administration in rats. Concurrent wheel access also speeds the extinction of, as well as prevents cocaine-primed reinstatement of, cocaine seeking behavior (Zlebnik et al., 2010). Additional studies found that 6 weeks of continual access to activity wheels decreases the reinforcing efficacy of intravenous cocaine as indexed by lower breakpoints under a progressive ratio schedule of reinforcement (Smith et al., 2008) or reduced escalation of intake during long daily access conditions (Smith et al., 2011). It was also the case that access to cocaine self-administration in turn suppressed wheel activity in either a concurrent-access (Cosgrove et al., 2002) or post-session (Smith et al., 2008) setting.

It remains unclear if spontaneous levels of activity are sufficient to reduce cocaine intake, since these prior studies examined the influence of wheel activity on cocaine self-administration in a way that likely increased the reinforcing value of wheel access. Rats provided continual access to an activity wheel increased running distances across 2–4 weeks (Eikelboom and Lattanzio, 2003; Smith et al., 2008). Lattanzio and Eikelboom showed that escalation in wheel activity occurred with 4 hrs or more, but not less than 2 hrs, of access

per day (Eikelboom and Lattanzio, 2003; Lattanzio and Eikelboom, 2003). This consistency with a popular model of “escalation” in drug self-administration studies (Ahmed and Koob, 1999) led some authors to posit this as an exercise-dependency model akin to substance dependence (Ferreira et al., 2006; Lattanzio and Eikelboom, 2003). An additional study showed that wheel activity increases after wheel access is discontinued for 24 hrs in rats previously given 30 days of continual access (Ferreira et al., 2006), consistent with the so-called deprivation effects observed with the self-administration of nicotine (O’Dell et al., 2007) and ethanol (Sinclair, 1979; Sinclair and Senter, 1968). Finally, the opiate antagonist naloxone induces more withdrawal signs in exercised than in sedentary rats (Kanarek et al., 2009). The available evidence is therefore consistent with wheel activity as a potential model of exercise dependence.

Exercise dependence can occur in humans, as defined in a manner consistent with the diagnosis of other behavioral disorders such as substance dependence. A sample of frequent gym attendees found that 42% were exercise dependent (Lejoyeux et al., 2008) based on criteria adapted from DSM-IV substance abuse criteria (Hausenblas and Giacobbi, 2004). Furthermore, habitual aerobic exercisers who stopped activity due to injury (Chan and Grossman, 1988) or were experimentally deprived of exercise (Modin et al., 1996) demonstrated mood disturbances (increased anxiety, depression and tension) consistent with drug withdrawal. The mood disruptions in the latter experimental study were attenuated when exercise was resumed. Lejoyeux and colleagues (2008) found that exercise-dependent individuals smoked less than non-dependent exercising individuals. It is therefore possible that dependence on exercise may be *required* to observe an effect of concurrent exercise on drug taking. Thus, the reduction in cocaine self-administration in the Cosgrove (2002) and Smith (2008, 2011) studies may have depended on the establishment of exercise dependence.

In the Smith (2008) study, wheel activity doubled across the first 2–3 weeks of 24-hr access. Cosgrove et al. (Cosgrove et al., 2002) provided an activity wheel for 6 hrs and only described a criterion for stability over at least 14 days; however, the report of Eikelboom and Lattanzio (Eikelboom and Lattanzio, 2003) suggests that wheel activity may significantly escalate over this interval with as little as 4 hr/day access. Thus, the observed suppressive effects of wheel access on cocaine self-administration (Cosgrove et al., 2002; Smith et al., 2008; Smith et al., 2011) may depend on increasing the relative reward value of wheel activity over its value in wheel-naïve animals. This has implications for the use of exercise in drug-use cessation trials and perhaps may explain variability in outcome across trials (Ussher et al., 2008).

The present study was conducted to determine if concurrent access to an exercise wheel could reduce intravenous d-methamphetamine self-administration in animals that had negligible prior wheel experience. This study extended prior studies that examined cocaine self-administration (Cosgrove et al., 2002; Smith et al., 2008; Smith et al., 2011; Zlebnik et al., 2010) to another stimulant drug of abuse and examined effects in male rats (only Smith (2011) found effects in male rats out of these prior studies). Experiments were conducted between groups in specialized operant chambers in which the wheel and METH were available concurrently, thereby combining the between-groups (Smith et al., 2008; Smith et al., 2011) and concurrent drug/wheel access (Cosgrove et al., 2002; Zlebnik et al., 2010) designs of the prior studies.

2. Materials and Methods

2.1 Subjects

Fifty four male Wistar (Charles River, NY) and thirteen Sprague Dawley (Harlan, Livermore, CA) rats served as subjects. Rats were 10 weeks old and weighed 200–250 grams upon arrival. They were housed in clear shoebox cages (2–3 rats per cage) in a vivarium with a 12:12 reverse light-dark cycle (lights off at 0800). Sessions (one per day) were conducted within the first 4 hours of the dark cycle and terminated after either 1 hour or 100 pellet deliveries (during lever-press training sessions) or 1 hour or 50 drug infusions (during self-administration sessions). Rats had free access to food pellets (Harlan Teklad LabDiet) and water throughout all experimental conditions except during the brief period of lever-press training as described below. Studies were conducted M-F and in accordance with the NIH Guide for the Care and Use of Laboratory Animals (Clark et al. 1996), and under protocols approved by the Institutional Animal Care and Use Committee (IACUC) of The Scripps Research Institute.

2.2 Apparatus

Activity wheels (35.6 cm diameter) attached to clear shoebox-style cages (48.26 cm × 26.67 cm × 20.32 cm) were used to collect baseline wheel activity (Med Associates Model ENV-046) prior to any other experimental manipulations. Each wheel revolution was equivalent to 1.12 meters. Basic operant conditioning chambers (Med Associates, St. Albans, VT, USA; Model ENV-007) were used during the lever-press training sessions. These chambers (55.9 cm × 55.9 cm × 40.6 cm) were enclosed in sound-attenuating cubicles, and were equipped with 2 levers, 2 stimulus lights, and a pellet aperture. Responses to the left lever produced access to 45 mg food pellets (TestDiet). Specialized operant conditioning chambers (Med Associates Model ENV-045) were used during the self-administration, concurrent-access, and wheel-only (control) conditions. These chambers were enclosed in sound-attenuating cubicles and equipped with slanted activity wheels (30 degree tilt and 60 cm diameter), 2 levers, 2 stimulus lights, a pellet aperture, and a drug infusion pump (Med Associates PHM-100-15). Each wheel revolution was equivalent to 1.88 meters. Equipment was controlled by MED-PC IV software.

2.3 Drug

D-methamphetamine (provided by RTI under contract to the National Institute on Drug Abuse) was dissolved in sterile saline and administered intravenously in a volume of 0.1 ml per infusion for self-administration and subcutaneously in a volume of 1 ml/kg for acute challenges.

2.4 Experimental Procedure

2.4.1 Assessment of Baseline Wheel Activity—All rats were initially given access to an activity wheel for two 1-hour sessions in order to establish baseline wheel activity. They were subsequently randomized into experimental groups based on their wheel activity.

2.4.2 Lever-Press Training—All rats were food restricted (15 g chow/day/rat) for 2 days prior to and throughout lever-press training (4–10 sessions). Responses on the left lever produced access to 45 mg pellets (TestDiet, 1811156) according to a fixed-ratio 1 (FR1) schedule of reinforcement. During the 10 sec time-out, the cue-light above the active lever was illuminated and responses on the inactive lever had no programmed consequences. Training was completed by meeting a criterion of 3 sessions with 100 pellets earned per session. Rats had no access to an activity wheel during this training.

2.4.3 Surgery and Catheter Maintenance—Male Wistar (N=30; Experiment 1) and Sprague Dawley (N=13; Experiment 2) rats were surgically implanted with an indwelling catheter in the right jugular vein as described in (Caine et al., 1993) with minor modifications (Emmett-Oglesby and Lane, 1992). Three groups of male Wistar control rats (N=8 per group) did not receive catheter implants. Briefly, rats were anesthetized with an isoflurane/oxygen vapor mixture (1.0–1.5%) and prepared surgically with chronic intravenous catheters, which consisted of a 14-cm length of silastic tubing attached to a guide cannula (Plastics One, Roanoke, VA). The cannula was curved to a right angle, encased in dental cement, anchored to a 3 cm circle of durable mesh, and implanted subcutaneously in the rat's back. Catheter tubing was passed subcutaneously to the right jugular vein where approximately 3.7 cm of the tubing was inserted into the vein and gently secured with suture thread. A liquid tissue adhesive was used to close incisions (3MTM VetbondTM Tissue Adhesive). During training and testing, catheters were flushed with sterile physiological saline containing either timentin (before sessions; 0.1 g/ml; 0.2–0.3 ml/rat) or heparin (after sessions; 10 USP units/ml; 0.2–0.3 ml/rat). Catheter patency was checked weekly after the last session by administering 0.2–0.3 ml of the ultra-short-acting barbiturate anesthetic Brevital sodium (1% methohexital sodium, Eli Lilly, Indianapolis, IN) through the catheter. Rats with patent catheters exhibited prominent signs of anesthesia (pronounced loss of muscle tone) within 3 sec of the Brevital injection. Failure to produce loss of muscle tone was considered a sign of a faulty catheter. In those cases, the rats were discontinued from the study, and all data subsequent to the last patency check were excluded from the analysis.

2.4.4 Self-Administration Training—All rats with catheter implants were trained to self-administer METH according to an FR1 schedule of reinforcement during single daily 1-hr sessions. Each response on the left lever activated the infusion pump for 4.33 seconds and delivered either 0.05 mg/kg/inf (for Wistar groups) or 0.10 mg/kg/inf (for Sprague Dawley groups) METH. A 20-s time-out ensued, with the illumination of a stimulus light while responses on either lever had no programmed consequences. Each session started with the stimulus light turned off.

2.4.5 Experiment 1: Concurrent-Access Testing (Wistar rats)—Male Wistar rats (14 weeks old and weighing on average 388 grams) self-administered METH (0.05 mg/kg/inf) for 21 days under an FR1 schedule in the following concurrent-access groups. One experimental group (hereafter referred to as Wheel_{1–14}) had access to both METH and an unlocked wheel for first 14 sessions, and thereafter had access to only METH (N=9); for a second group (Wheel_{8–21}) METH was available during sessions 1–7 (wheel was locked) and then concurrent access to both METH and an unlocked wheel were available during sessions 8–21 (N=11); the third group (Wheel_{15–21}) had access to METH only during the first 14 sessions (wheel was locked) but then had concurrent access to both METH and an unlocked wheel during sessions 15–21 (N=10). Control groups of male Wistar rats (without intravenous catheters) were tested in 1-hr sessions wherein one group (NoMeth_{1–14}) had access to an activity wheel for 14 sessions (N=8); for the second group (NoMeth_{8–21}) the activity wheel was locked during sessions 1–7 and then unlocked during sessions 8–21 (N=8); for the third group (NoMeth_{15–28}) the activity wheel was locked during sessions 1–14 and then unlocked during sessions 15–28 (N=8). (Data from session 4 for the NoMeth_{1–14} group were excluded from analysis due to inadvertent vivarium disruptions prior to that session.) For the control groups, the levers were extended and completion of the FR1 resulted in the presentation of the stimulus light only. After the conclusion of the 28 sessions, the NoMeth_{15–28} group was challenged s.c. with 0, 0.56, 1.0 and 5.6 mg/kg METH administered just prior to sessions in the wheel chambers. Doses were administered in a Latin Square design with 3–4 days between challenges.

2.4.6 Experiment 2: Concurrent-Access Testing (Sprague Dawley rats)—The second experiment was conducted to confirm the generality of effects of concurrent availability of wheel access and METH on self-administration. For this purpose, male Sprague Dawley rats (16 weeks old and weighing on average 382 grams) were selected because this strain tends to be less active in open field locomotion and also tends to self-administer slightly more stimulant drug. The per-infusion dose of METH was also increased to 0.1 mg/kg/inf. Together these changes were hypothesized to shift the relative preferences for wheel activity and drug intake toward drug self-administration, in comparison with the first experiment. This study included two groups: one that had concurrent access to both METH and an unlocked wheel for 14 sessions (N=7), hereafter referred to as group Sprague Dawley Wheel1–14 (or SD.Wheel_{1–14}); the second group had access to METH but the wheel was locked for 14 sessions (SD.NoWheel_{1–14}; N=6).

2.5 Data Analysis

Analysis of the drug-infusion and wheel quarter rotation data employed analysis of variance (ANOVA) with between-subjects factors of treatment Group and within-subjects factors of Sessions and drug treatment condition as detailed in the Results for each experiment. Post-hoc analyses of significant main effects in the ANOVA were conducted using the Fisher's LSD test including all pairwise comparisons; the criterion for significance was $p < 0.05$. Analyses were conducted with GB-STATv7.0; Dynamic Microsystems, Silver Spring, MD.

3. RESULTS

3.1 Experiment 1: Concurrent-Access Testing (Wistar rats)

3.1.1 Effects of Wheel Activity on Self-Administration—Wistar rats with concurrent access to an activity wheel from the start of self-administration (Wheel_{1–14}) took significantly less METH compared with the other two Wistar intravenous self-administration (IVSA) groups (Figure 1) as was confirmed by a main effect of group ($F_{2,27}=3.57$; $p < 0.05$) on the ANOVA covering the first 14 sessions. The post-hoc test further confirmed significant differences between the Wheel_{1–14} and the Wheel_{15–21} groups on sessions 1, 3, 4, 6, 9 and 11. The 14-session concurrent METH and wheel-access group (Wheel_{1–14}) differed from the Wheel_{8–14} group on sessions 1, 2, 3, 5, 6, 7 and 8. The groups with concurrent METH and wheel access on sessions 15–21 (Wheel_{15–21}) and on sessions 8–14 (Wheel_{8–21}) differed significantly only on the first day of METH access. There was no main effect of session in this analysis.

3.1.2 Effects of Changes in Wheel-Access Conditions on Self-Administration—To determine if changes in the wheel-access condition affected METH self-administration, the cumulative intake of drug across 7-session bins was analyzed (Figure 2). Analysis of the first 14 sessions for the groups with concurrent access (Wheel_{1–14}), METH only (no wheel access, i.e., Wheel_{15–21}) or METH only during sessions 1–7 and concurrent access during sessions 8–14 (i.e., Wheel_{8–21}) showed a significant main effect of group ($F_{2,27}=3.51$; $p < 0.05$) but not of bin (sessions 1–7 vs sessions 8–14), nor any interaction. The post-hoc analysis confirmed that cumulative METH intake was lower in the Wheel_{1–14} group compared with the two other groups (Wheel_{8–21} and Wheel_{15–21}) in the first 7 sessions and compared to the Wheel_{15–21} group for sessions 8–14. A similar analysis was conducted to determine the effect of discontinuing wheel access in the Wheel_{1–14} group and adding wheel access in the Wheel_{15–21} group by comparing cumulative intake in sessions 8–14 and 15–21 for each of the three groups. No significant main effects of group or bin were confirmed.

3.1.3 Effects of Self-Administration on Wheel Activity—Access to METH self-administration significantly altered the amount of wheel activity in the Wistar rats (Figure 3). The omnibus three-factor analysis compared quarter rotations across the first 7 sessions (the maximum duration for the Wheel_{15–21} group) in which the wheel was unlocked for METH self-administering groups (Wheel_{1–14}, Wheel_{8–21} and Wheel_{15–21}) and non-drug controls (NoMeth_{1–14}, NoMeth_{8–21}, NoMeth_{15–28}). The ANOVA confirmed main effects of sessions ($F_{6,60} = 3.3$; $p < 0.01$), of METH/NoMeth group ($F_{1,10} = 18.0$; $p < 0.005$) as well as for the interaction of drug-access with session ($F_{6,60} = 3.5$; $p < 0.01$), the time wheel access was initiated (session 1, 8 or 15) with drug-access ($F_{2,20} = 4.8$; $p < 0.001$) as well as a three-way interaction of all factors ($F_{12,120} = 3.5$; $p < 0.0005$).

The data were further analyzed by two-factor ANOVA to determine if the alteration in running was associated with the time wheel access was initiated. One analysis was conducted for the initial 7 session of wheel access for METH self-administering groups and a second analysis was conducted for the initial 14 days of wheel access for the non-drug control groups. Analysis of the METH self-administering groups confirmed a significant main effect of groups distinguished by the day of wheel initiation ($F_{2,27} = 4.8$; $p < 0.05$). The post-hoc test confirmed that wheel activity was lower in the Wheel_{8–21} group for sessions 8–11 and 13, and for the Wheel_{15–21} group for all 7 sessions, when compared with the Wheel_{1–14} group. This analysis also confirmed that within-group, activity was lower in the Wheel_{1–14} group on sessions 5 and 7 compared with the first session and higher in the Wheel_{15–21} group on session 20 compared with their first day of wheel access (overall session 15).

The analysis of the NoMeth control groups confirmed a significant interaction between the time wheel access was initiated and session ($F_{26,273} = 1.8$; $p < 0.05$). The post hoc test confirmed that wheel activity differed between the NoMeth_{1–14} and NoMeth_{8–21} groups on the first, tenth, twelfth and thirteenth session of wheel access, between the NoMeth_{1–14} and NoMeth_{15–28} groups on the first and eighth sessions of wheel access and between NoMeth_{8–21} and NoMeth_{15–28} groups on the twelfth and thirteenth session of wheel access. Systematic changes in activity within group were also confirmed. In comparison with their first day of access, the NoMeth_{1–14} group ran more on sessions 5, 8 and 12, the NoMeth_{8–21} group ran less on session 13 and the NoMeth_{15–28} group ran less on sessions 18, 20–23 and 26–27.

The final set of two-factor follow-up analyses were conducted to determine differences between METH self-administering groups and their respective control groups in separate analyses for those groups in which wheel access was initiated on sessions 1, 8 and 15. A significant interaction between drug-access and Sessions was confirmed for the session 1–14 groups ($F_{13,195} = 2.2$; $p < 0.05$) and the posthoc test confirmed wheel running only differed between the groups on session 1 (lower for control rats) and 13 (lower for METH self-administering rats). Wheel activity for METH self-administering rats was lower in sessions 10, 12–13 compared to their own first session, and in the NoMeth control group activity was *higher* on sessions 3 and 5, relative to the first session. A significant main effect of wheel-access session was confirmed for the session 8–21 groups ($F_{13,221} = 2.4$; $p < 0.01$) and the posthoc test further confirmed that wheel activity was higher in sessions 19 and 20 compared with the first session for the METH group and in session 19 for the control group. Finally, main effect of drug-access group ($F_{1,16} = 8.5$; $p < 0.05$) and a significant interaction between drug-access and sessions was confirmed for the session 15–21 groups ($F_{6,96} = 6.2$; $p < 0.0001$). The posthoc test confirmed the METH self-administering group had less activity in all 7 sessions compared with the control group and ran more on sessions 17–21 compared with their first day of wheel access. In contrast, the control group ran less on the wheel in sessions 17–18 and 20–21 compared with their first day of wheel access.

3.1.4 Effects of Acute METH Challenge on Wheel Activity—The NoMeth_{15–28} control group was challenged with vehicle and three doses of METH (0.56, 1.0, 5.6 mg/kg; s.c.) in a randomized, repeated measures design (Figure 4). The lower end of this dose range overlaps with the cumulative (i.v.) intake of self-administering rats and the higher end has been previously shown to decrease wheel activity (Gilpin et al., 2011). We have previously shown increased wheel activity after 1.0 mg/kg METH and decreased wheel activity after 5.6 mg/kg METH in a prior study (Gilpin et al., 2011). There was no main effect of drug treatment dose ($F_{3,21} = 2.8$; $p = 0.066$) confirmed in the repeated measures ANOVA but this may be because an apparent stimulant effect was observed in 5/8 animals and at different doses (0.56, 1.0 mg/kg). Decreases in wheel activity relative to the vehicle condition were observed in 4/8 animals after at least one METH dose.

3.2 Experiment 2: Concurrent-Access Testing (Sprague Dawley rats)

3.2.1 Effects of Wheel Activity on Self-Administration—Results similar to those of Experiment 1 were observed in the Sprague Dawley rats with 14 sessions of concurrent access to both METH and an unlocked activity wheel (SD.Wheel_{1–14}) or to METH and a locked wheel (SD.NoWheel_{1–14}). Overall the intended difference in drug/wheel preference was obtained because Sprague Dawley rats in this experiment self-administered more infusions of METH than did the Wistar rats and had one-sixth as much wheel activity (Figure 5). In addition, the wheel pre-screening sessions conducted prior to the study showed that Sprague Dawley rats ran about half as much as Wistar rats (data not shown). As with the Wistar groups, a significant main effect of treatment group ($F_{1,11} = 16.78$; $p < 0.005$) was confirmed for the Sprague Dawley rats; the post-hoc test confirmed significant group differences in sessions 2, 4, 7 and 10–14. In contrast to the Wistar groups, however, the SD.NoWheel_{1–14} group took more infusions in sessions 11–13 compared with the 1st session.

4. Discussion

This study demonstrates that when male rats have concurrent access to an activity wheel from the start of intravenous self-administration, they will initially take less methamphetamine (METH). The present results are consistent with previous studies that examined wheel access and drug self-administration (Cosgrove et al., 2002; Smith et al., 2008; Smith et al., 2011; Zlebnik et al., 2010) but significantly extend those prior findings with cocaine self-administration. First, it was shown that concurrent access to an activity wheel reduced the intravenous self-administration of an additional stimulant drug of abuse, METH. Second, the effect was observed in rats that had negligible prior exposure to activity wheels. This is important since a gradual escalation in the amount rats will run on wheels over 10–20 sessions of continual access may be caused by a shift in the reinforcing value of wheel activity (Ferreira et al., 2006; Kanarek et al., 2009; Lattanzio and Eikelboom, 2003). Third, these data demonstrate a suppressing effect of the concurrent opportunity for exercise on METH self-administration in *male* rats; only Smith et al (2011) have reported similar effects for cocaine self-administration in males. Finally, the generality of the effect of concurrent wheel access was confirmed in two strains of rats which differ significantly in their spontaneous preference for wheel activity.

The present data also show, conversely, that concurrent access to self-administered METH reduces wheel activity. The Wistar group with concurrent access to the wheel and METH for the initial 14 sessions exhibited stable drug intake, but wheel activity was significantly reduced at the end of this interval, relative to the start. Wheel activity was also significantly reduced in different groups of rats that received 7 or 14 self-administration sessions prior to the wheels being unlocked, relative to the group with concurrent unlocked wheels and

METH access from the 1st session. A similar within-group effect was demonstrated for concurrent cocaine self-administration by Cosgrove and colleagues (2002). Likewise, the recent Smith et al (2011) paper showed that wheel activity in the ~22 hrs outside of the operant chamber was reduced after 23 hr cocaine binge sessions but then recovered to baseline levels over several days of only 2hr cocaine access. The present data extend these observations by showing both between and within groups that wheel activity depends on the duration of prior METH experience.

Interpretation of a specific effect of concurrent METH self-administration on wheel activity is further strengthened by the results from the control groups, which were provided with wheel but not drug access. Prior studies did not have such wheel-activity control groups and therefore could not rule out possible habituation effects. In the present study, the within-group decrease in activity was not observed in the control group of rats that had access to wheel (but not drug) in the first 14 sessions in the operant chambers. The groups of rats that were allowed to explore the operant box and operate the levers for 7 or 14 sessions with the wheel locked subsequently ran more than the respective groups allowed access to METH for 7 or 14 sessions prior to concurrent-wheel access. These controls indicate that the within-group and between-group reductions in wheel activity observed in the METH self-administering groups were unlikely to be due to habituation to the operant box or the wheel itself. Thus, the most plausible interpretation of these data is that ongoing access to self-administered METH reduces the reinforcing value of the wheel relative to its reinforcing value when METH is not experienced. Kanarek and colleagues similarly found that wheel activity was suppressed after 13 (but not 7) sessions of oral amphetamine (Kanarek et al., 1995).

The experimenter-administered METH challenges in the NoMETH₁₅₋₂₈ control group (Figure 4) provides evidence that the reduction in wheel activity in the self-administering groups was not due to induction of repetitive, stereotypical behavior. It should be noted that stereotypies were not observed in the self-administering animals upon removal from the chamber. Mean cumulative intakes in the Wistar groups were about 0.25–0.65 mg/kg; our prior acute challenge study (Gilpin et al., 2011) showed that wheel activity is increased after 1.0 mg/kg METH, s.c., and decreased after 5.6 mg/kg. Those prior data used a different wheel arrangement but the data in Figure 4 in the chamber/wheel trained control group show a similar profile. The administration of 0.56–1.0 mg/kg *increased* mean wheel activity and increased activity in a majority of individuals. Suppression of activity was only observed in one individual after 1.0 mg/kg. Although these acute challenge data differ in route of administration, contingent versus noncontingent administration and bolus versus incremental accumulation, it still appears reasonable to predict that any direct locomotor effect of self-administered METH would not be likely to decrease wheel activity.

One potential limitation in the interpretation of the present results is that relative value of the wheel may change as a function of age in the rat. This seems unlikely, however, given that the rats in the present study ranged from about 2–5 months of age across the entire interval of study. Prior work shows no difference in efficacy of wheel access as a reinforcer across studies with rats of ages from about 2 months to 25 months of age (Belke, 2006, 2010; Belke and Hancock, 2003; Belke et al., 2005; Pierce et al., 1986). Other work has shown essentially no difference in physiological adaptation to many weeks of forced treadmill exercise up to 24 months of age (Mazzeo et al., 1984; Rossiter et al., 2005) and no decline in voluntary wheel activity until past 9 months of age (Holloszy et al., 1985). Perhaps most pertinently, the fact that each of the control groups ran about as much in their first few session of wheel access as did the Meth₁₋₁₄ group shows that the several weeks difference in this study did not affect the value of wheel activity.

A further consideration for all studies of this type lies in the fact that wheel activity can be a dependent variable, an operant behavioral response and a reinforcing event. This is a necessary complication of any similar model in laboratory rodents given the spontaneous activity exhibited by most strains of common laboratory species when provided a wheel. It can often be difficult to gain definitive estimates of the reinforcing efficacy of any stimulus, but synthesis of converging methods can be helpful. In the current study, wheel activity was a recorded response; however, within the context of METH self-administration, it may function as a reinforcer that directly competed with (the reinforcing efficacy of) METH, thereby decreasing drug self-administration. Previous findings from cocaine self-administration studies using rodent models support this inference (Cosgrove et al., 2002; Smith et al., 2008; Smith et al., 2011; Zlebnik et al., 2010).

This study was conducted within a context of determining if a healthy alternative to drug use—physical exercise—can be therapeutic for METH abuse. The most common manipulation (i.e., introduction of the wheel after 7 or 14 self-administration sessions) did not alter METH intake within group. This result is unlike the effects of introducing wheel access in rats bred for high ethanol preference in which oral ethanol intake was reduced (McMillan et al., 1995). These effects are also dissimilar to those of Cosgrove and colleagues who showed that introduction of concurrent wheel access reduced cocaine intake relative to the prior 5 days of access to cocaine without the wheel (Cosgrove et al., 2002). In the Cosgrove study, however, the rats had been pre-conditioned to the wheel in 6-hour sessions for at least 14 sessions and until stability criteria were obtained; the data are not shown but escalated activity is very likely in this context (Eikelboom and Lattanzio, 2003).

A substantial amount of evidence shows that there is an inverse relation between exercise and drug use. That is, both animal (Cosgrove et al., 2002; Smith et al., 2008; Smith et al., 2011; Zlebnik et al., 2010) and human studies show that exercise predicts lower drug consumption, whereas restriction from exercise increases the likelihood of drug use (Carroll and Boe, 1982; Hosseini et al., 2009; Lejoyeux et al., 2008; Pate et al., 2000) and other maladaptive traits, such as mood disturbances (Modin et al., 1996) and psychological distress (Chan and Grossman, 1988). Thus, exercise programs may protect individuals from drug use. The present results confirm some potential for non-dependent levels of exercise to attenuate drug taking. It continues to be worthwhile to investigate the conditions under which exercise influences the propensity for drug use, with an emphasis on translating preclinical results into clinical practice for the treatment of drug abuse.

In summary, these data provide additional evidence from an animal model that concurrent access to physical exercise can reduce the amount of methamphetamine that is self-administered. In this context it is not necessary to pre-train the rats to an escalated activity level before drug to observe the effect, unlike prior demonstrations of effects on cocaine self-administration (Cosgrove et al., 2002; Smith et al., 2008; Smith et al., 2011; Zlebnik et al., 2010). This study also shows that exposure to a stimulant drug can interfere with the value of *exercise* as a reinforcer. As such, this may serve as a model to evaluate the preservation of the relative value of alternative reinforcers in the context of ongoing recreational drug use.

Acknowledgments

Role of Funding Source: The study was conducted under the support of USPHS grants DA018418, DA024105 and DA024705 (MAT), and NIH/NIGMS Award T34GM087193 (BDV). The NIH/NIDA had no role in study design, collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. The authors have no conflicts of interest to report for this study.

This is publication #21243 from The Scripps Research Institute.

References

- Ahmed S, Koob G. Long-lasting increase in the set point for cocaine self-administration after escalation in rats. *Psychopharmacology (Berl)*. 1999; 146:303–312. [PubMed: 10541731]
- Belke TW. Running and responding reinforced by the opportunity to run: effect of reinforcer duration. *J Exp Anal Behav*. 1997; 67:337–351. [PubMed: 9163938]
- Belke TW. Varying wheel-running reinforcer duration within a session: effect on the revolution-postreinforcement pause relation. *J Exp Anal Behav*. 2000; 73:225–239. [PubMed: 10784011]
- Belke TW. Responding for sucrose and wheel-running reinforcement: effect of body weight manipulation. *Behav Process*. 2004; 65:189–199.
- Belke TW. Responding for sucrose and wheel-running reinforcement: effect of pre-running. *Behav Process*. 2006; 71:1–7.
- Belke TW. Exclusive preference develops less readily on concurrent ratio schedules with wheel-running than with sucrose reinforcement. *J Exp Anal Behav*. 2010; 94:135–158. [PubMed: 21451744]
- Belke TW, Dunbar MJ. Effects of cocaine on fixed-interval responding reinforced by the opportunity to run. *J Exp Anal Behav*. 2001; 75:77–91. [PubMed: 11256868]
- Belke TW, Hancock SD. Responding for sucrose and wheel-running reinforcement: effects of sucrose concentration and wheel-running reinforcer duration. *J Exp Anal Behav*. 2003; 79:243–265. [PubMed: 12822690]
- Belke TW, Oldford AC, Forgie MY, Beye JA. Responding for sucrose and wheel-running reinforcement: effect of D-amphetamine. *Behav Pharmacol*. 2005; 16:219–225. [PubMed: 15961961]
- Caine SB, Lintz R, Koob GF. Intravenous drug self-administration techniques in animals. In: Sahgal, A., editor. *Behavioral Neuroscience: A Practical Approach*. Oxford University Press; New York, NY: 1993. p. 117–143.
- Carroll ME, Boe IN. Increased intravenous drug self-administration during deprivation of other reinforcers. *Pharmacol Biochem Behav*. 1982; 17:563–567. [PubMed: 6128744]
- Chan C, Grossman H. Psychological Effects of Running Loss on Consistent Runners. *Percept Mot Skills*. 1988; 66:875–883. [PubMed: 3405713]
- Collier G, Hirsch E. Reinforcing properties of spontaneous activity in the rat. *J Comp Physiol Psychol*. 1971; 77:155–160. [PubMed: 5120680]
- Cosgrove KP, Hunter RG, Carroll ME. Wheel-running attenuates intravenous cocaine self-administration in rats: sex differences. *Pharmacol Biochem Behav*. 2002; 73:663–671. [PubMed: 12151042]
- Eikelboom R, Lattanzio SB. Wheel access duration in rats: II. day-night and within-session changes. *Behav Neurosci*. 2003; 117:825–832. [PubMed: 12931966]
- Emmett-Oglesby MW, Lane JD. Tolerance to the reinforcing effects of cocaine. *Behav Pharmacol*. 1992; 3:193–200. [PubMed: 11224116]
- Ferreira A, Lamarque S, Boyer P, Perez-Diaz F, Jouvent R, Cohen-Salmon C. Spontaneous appetite for wheel-running: a model of dependency on physical activity in rat. *Eur Psychiatry*. 2006; 21:580–588. [PubMed: 17161285]
- Forristall JR, Hookey BL, Grant VL. Conditioned taste avoidance induced by forced and voluntary wheel running in rats. *Behav Process*. 2007; 74:326–333.
- Gilpin NW, Wright MJ Jr, Dickinson G, Vandewater SA, Price JU, Taffe MA. Influences of activity wheel access on the body temperature response to MDMA and methamphetamine. *Pharmacol Biochem Behav*. 2011; 99:295–300. [PubMed: 21605589]
- Hausenblas H, Giacobbi P. Relationship between exercise dependence symptoms and personality. *Pers Individ Diff*. 2004; 36:1265–1273.
- Holloszy JO, Smith EK, Vining M, Adams S. Effect of voluntary exercise on longevity of rats. *J Appl Physiol*. 1985; 59:826–831. [PubMed: 4055572]
- Hosseini M, Alaei HA, Naderi A, Sharifi MR, Zahed R. Treadmill exercise reduces self-administration of morphine in male rats. *Pathophysiology*. 2009; 16:3–7. [PubMed: 19131225]

- Hundt AG, Premack D. Running as both a positive and negative reinforcer. *Science*. 1963; 142:1087–1088. [PubMed: 14068233]
- Kanarek RB, D'Anci KE, Jurdak N, Mathes WF. Running and addiction: precipitated withdrawal in a rat model of activity-based anorexia. *Behav Neurosci*. 2009; 123:905–912. [PubMed: 19634951]
- Kanarek RB, Marks-Kaufman R, D'Anci KE, Przypek J. Exercise attenuates oral intake of amphetamine in rats. *Pharmacol Biochem Behav*. 1995; 51:725–729. [PubMed: 7675851]
- Lattanzio SB, Eikelboom R. Wheel access duration in rats: I. effects on feeding and running. *Behav Neurosci*. 2003; 117:496–504. [PubMed: 12802878]
- Lejoyeux M, Avril M, Richoux C, Embouazza H, Nivoli F. Prevalence of exercise dependence and other behavioral addictions among clients of a Parisian fitness room. *Compr Psychiatry*. 2008; 49:353–358. [PubMed: 18555055]
- Marcus BH, Albrecht AE, King TK, Parisi AF, Pinto BM, Roberts M, Niaura RS, Abrams DB. The efficacy of exercise as an aid for smoking cessation in women: a randomized controlled trial. *Arch Intern Med*. 1999; 159:1229–1234. [PubMed: 10371231]
- Masaki T, Nakajima S. Forward conditioning with wheel running causes place aversion in rats. *Behav Process*. 2008; 79:43–47.
- Mazzeo RS, Brooks GA, Horvath SM. Effects of age on metabolic responses to endurance training in rats. *J Appl Physiol*. 1984; 57:1369–1374. [PubMed: 6520029]
- McMillan DE, McClure GY, Hardwick WC. Effects of access to a running wheel on food, water and ethanol intake in rats bred to accept ethanol. *Drug Alcohol Depend*. 1995; 40:1–7. [PubMed: 8746918]
- Modin G, Morgan W, Piering P, Stenger A, CLS, Trine M, WUM. Psychological consequences of exercise deprivation in habitual exercisers. *Med Sci Sports Exerc*. 1996; 28:1199–1203. [PubMed: 8883010]
- O'Dell SJ, Gross NB, Fricks AN, Casiano BD, Nguyen TB, Marshall JF. Running wheel exercise enhances recovery from nigrostriatal dopamine injury without inducing neuroprotection. *Neuroscience*. 2007; 144:1141–1151. [PubMed: 17157992]
- Pate R, Trost S, Levin S, Dowda M. Sports participation and health-related behaviors among US youth. *Arch Pediatr Adolesc Med*. 2000; 154:904–911. [PubMed: 10980794]
- Pierce WD, Epling WF, Boer DP. Deprivation and satiation: the interrelations between food and wheel running. *J Exp Anal Behav*. 1986; 46:199–210. [PubMed: 16812460]
- Premack D, Schaeffer RW, Hundt A. Reinforcement of drinking by running: effect of fixed ratio and reinforcement time. *J Exp Anal Behav*. 1964; 7:91–96. [PubMed: 14120150]
- Rossiter HB, Howlett RA, Holcombe HH, Entin PL, Wagner HE, Wagner PD. Age is no barrier to muscle structural, biochemical and angiogenic adaptations to training up to 24 months in female rats. *J Physiol*. 2005; 565:993–1005. [PubMed: 15845588]
- Sherwin CM. Voluntary wheel running: a review and novel interpretation. *Anim Behav*. 1998; 56:11–27. [PubMed: 9710457]
- Sinclair JD. Alcohol-deprivation effect in rats genetically selected for their ethanol preference. *Pharmacol Biochem Behav*. 1979; 10:597–602. [PubMed: 572554]
- Sinclair JD, Senter RJ. Development of an alcohol-deprivation effect in rats. *Q J Stud Alcohol*. 1968; 29:863–867. [PubMed: 5705408]
- Smith MA, Schmidt KT, Iordanou JC, Mustroph ML. Aerobic exercise decreases the positive-reinforcing effects of cocaine. *Drug Alcohol Depend*. 2008; 98:129–135. [PubMed: 18585870]
- Smith MA, Walker KL, Cole KT, Lang KC. The effects of aerobic exercise on cocaine self-administration in male and female rats. *Psychopharmacology (Berl)*. 2011 May 13. epub ahead of print.
- Taliaferro LA, Rienzo BA, Donovan KA. Relationships between youth sport participation and selected health risk behaviors from 1999 to 2007. *J Sch Health*. 2010; 80:399–410. [PubMed: 20618623]
- Ussher MH, Taylor A, Faulkner G. Exercise interventions for smoking cessation. *Cochrane Database Syst Rev*. 2008:CD002295. [PubMed: 18843632]

Zlebnik N, Anker J, Gliddon L, Carroll M. Reduction of extinction and reinstatement of cocaine seeking by wheel running in female rats. *Psychopharmacology (Berl)*. 2010; 209:113–125. [PubMed: 20112008]

Figure 1.

Mean number of d-methamphetamine infusions (METH; 0.05 mg/kg/inf) per session for groups of male Wistar rats trained to self-administer under an FR1 schedule of reinforcement. These groups include those with access to unlocked wheels for the first 14 sessions (Wheel₁₋₁₄; N = 9) or for sessions 8–14 (Wheel₈₋₂₁; N = 11), and those without access to unlocked wheels for the first 14 sessions (Wheel₁₅₋₂₁; N = 10). A significant difference between the groups with and without access to unlocked wheels is indicated by * and from the Wheel₈₋₂₁ group by #. Bars indicate $\pm$ SEM.

Figure 2.

Cumulative d-methamphetamine intake across 7-session bins for Wistar rat groups depicted in Figure 1. The transition from concurrent access to METH only (no wheel) for the Wheel₁₋₁₄ group is shown by the black bar; the transition from METH only (no wheel) to concurrent access is shown by the gray and black bars for the Wheel₈₋₂₁ group and by the black bar for the Wheel₁₅₋₂₁ group. Bars indicate $\pm$ SEM.

Figure 3.

Mean number of quarter revolutions on activity wheels across sessions for groups of Wistar rats trained to self-administer 0.05 mg/kg/inf METH with concurrent access to unlocked wheels, either during sessions 1–14 (upper panel; Wheel₁₋₁₄; N=9), during sessions 8–21 (middle panel; Wheel₈₋₂₁; N=11), or during sessions 15–21 (lower panel; Wheel₁₅₋₂₁; N=11), and the respective control groups that received no METH. The control groups had access to unlocked wheels for 14 sessions, either during sessions 1–14 (NoMeth₁₋₁₄; N=8), sessions 8–21 (NoMeth₈₋₂₁; N=8), or sessions 15–28 (NoMeth₁₅₋₂₈; N=8). Significant differences between METH and NoMeth control groups are shown by *, between Wheel₁₋₁₄ and other METH groups by ‡, between the NoMeth₁₋₁₄ group and the other NoMeth groups by \$ and differences from the first session within-group by #. Bars indicate $\pm$ SEM.

Figure 4.

Mean number of quarter revolutions on activity wheel as a function of d-methamphetamine challenges (0.56, 1.0, and 5.6 mg/kg) and vehicle for the NoMeth15–28 Wistar rats (N=8). Group data are shown in the upper panel; individual data are shown in the lower panel. Bars indicate $\pm$ SEM.

Figure 5.

Mean ($\pm$ SEM) number of METH infusions (0.1 mg/kg/inf) per session for groups of male Sprague Dawley rats trained to self-administer under an FR1 schedule of reinforcement (upper panel). These groups include those with (SD.Wheel₁₋₁₄; N = 6) and without (SD.NoWheel₁₋₁₄; N = 7) access to unlocked wheels for the first 14 sessions. A significant difference between the groups is indicated by * and a difference relative to the first session within group is indicated by #. Mean ($\pm$ SEM) wheel activity for the SD.Wheel₁₋₁₄ group is contrasted with the wheel activity for the Wheel₁₋₁₄ Wistar rat group depicted in Figure 3.