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Pharmacology, Biochemistry and Behavior 73 (2002) 663–671

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Wheel-running attenuates intravenous cocaine self-administration in rats Sex differences

Kelly P. Cosgrove, Robb G. Hunter, Marilyn E. Carroll*

Department of Psychiatry, University of Minnesota, Mayo Box 392, Minneapolis, MN 55455, USA

Received 15 January 2002; received in revised form 17 April 2002; accepted 29 April 2002

Abstract

This experiment examines the effect of access to a running-wheel on intravenous cocaine self-administration in male and female rats. Rats maintained at 85% of their free-feeding body weight were first exposed to the running-wheel alone during the 6-h sessions until behavior stabilized for 14 days. Intravenous cannulae were then implanted, and the rats were trained to self-administer a low dose of cocaine (0.2 mg/kg) under a fixed-ratio (FR 1) schedule during the 6-h sessions, while the wheel remained inactive and cocaine self-administration stabilized (cocaine-only condition). Next, the wheel access and cocaine self-administration were concurrently available followed by a period of cocaine-only. Behavior was allowed to stabilize for 10 days at each phase. During wheel access, cocaine infusions decreased by 21.9% in males and 70.6% in females compared to the cocaine-only condition; the effect was statistically significant in females. Infusions increased to baseline levels when wheel access was terminated. When cocaine infusions were concurrently available, wheel revolutions were reduced by 63.7% and 61.5% in males and females, respectively, compared to the wheel-only condition. This result did not differ due to sex, but it was statistically significant when data from males and females were combined. These results indicate that wheel-running activity had a greater suppressant effect on cocaine self-administration in females than in males, and in females, wheel-running and cocaine self-administration are substitutable as reinforcers.

Keywords: Alternative reinforcer; Cocaine; Exercise; Intravenous; Rat; Self-administration; Sex; Substitution; Wheel-running

1. Introduction

Enriching the environment with alternative nondrug reinforcers is a promising approach to reducing the initiation, maintenance and reinstatement of drug abuse (Bardo et al., 2001; Carroll, 1996; Carroll et al., 2001a,b; Klebauer et al., 2001). In animal studies, environmental enrichments have typically consisted of consummatory rewards such as preferred food or sweetened liquids (Carroll et al., 2001a); however, nonconsummatory environmental stimuli can also decrease drug self-administration. For example, rats exposed to novel plastic objects decreased their rate of acquisition of amphetamine self-administration (Bardo et al., 2001; Klebauer et al., 2001). Similarly, a social (vs. isolated) environment inhibits drug self-administration (Alexander et al., 1978; Bardo et al., 2001; Hadaway et al., 1979; Schenk et al., 1987). In contrast, isolation or social stress increases the acquisition of drug self-administration (Haney et al., 1995; Ramsey, 1991).

There are also a number of human laboratory studies that support the reduction in drug self-administration by presentation of nondrug alternative reinforcers (e.g., Bickel et al., 1997; Higgins, 1997; Higgins et al., 1994a,b; West et al., 1999). Clinical applications of this approach have used money (Comer et al., 1998; Hart et al., 2000; Hatsukami et al., 1994; Heishman et al., 2000), jobs (Silverman et al., 1996a,b) or vouchers that can be traded for commodities, social events, etc. (Budney et al., 1999; Higgins, 1997; Higgins et al., 1994a,b; Silverman et al., 1996a,b, 1998, 1999). In the present investigation, the alternative nondrug reinforcer was running-wheel activity. There is some limited evidence that exercise aids humans in smoking cessation (Ussher et al., 2000, 2001), and exercise is a nondrug alternative activity that has also been related to reductions in drug consumption. For example, access to a running wheel reduces oral intake of amphetamine in rats (Kanarek et al., 1995) and ethanol drinking in ethanol-preferring rats (McMillan et al., 1995). The application of

* Corresponding author. Tel.: +1-612-626-6289; fax: +1-624-8935.
E-mail address: mcarroll@umn.edu (M.E. Carroll).

0091-3057/02/$ – see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0091-3057(02)00853-5

exercise as an alternative to drug taking may be advantageous over ingestion of preferred dietary substances in animals or monetary (voucher) rewards in humans, as it is healthier than eating palatable foods and is less expensive.

Wheel-running in rodents can function as a reinforcing event, as rats will perform instrumental responses to gain access to running wheels (Catania, 1966; Epling and Pierce, 1992; Iversen, 1993; Premack, 1972). In fact, when given a choice between food and running wheels, rats often choose running over food (Epling and Pierce, 1992; Routtenberg, 1968; Symons, 1973). It has been hypothesized that wheel-running and drug self-administration activate the same brain reward mechanisms that are associated with eating, drinking and sex (Serwatkiewicz et al., 2000; Sherwin, 1998; Werme et al., 1999, 2000). Wheel-running in rats has motivational features in common with feeding behavior, and they may function as substitutes. Rats deprived of food run more than nondeprived controls (Finger, 1951; Pierce et al., 1986; Symons, 1973; Treichler and Hall, 1962), and food consumption decreases on days that rats have access to running wheels (Mueller et al., 1997). Activity-based anorexia occurs when rats are fed one meal per day and allowed access to a running wheel for the rest of the day (Pierce et al., 1986; Routtenberg and Kuznesof, 1967; Spear and Hill, 1962). There is evidence that wheel-running stimulates endogenous opioids, as opioid antagonists decrease running wheel activity (Lett et al., 2001; Sisti and Lewis, 2001) and suppress the increases in dynorphin mRNA in the medial caudate putamen after running-wheel activity (Werme et al., 2000).

There is also evidence for an interaction between running-wheel activity and the effects of drugs of abuse. In mice artificially selected for increased voluntary wheel-running, the high-running mice were also hyperactive. In these mice, cocaine and the dopamine reuptake inhibitor, GBR 12909, reduced wheel-running in hyperactive animals, but running had no effect on control-line animals (Rhodes et al., 2001). Thus, the relationship between wheel-running and effects of drugs of abuse may covary with general activity (e.g., Mantsch et al., 2001; Piazza et al., 1989; Suto et al., 2001), compulsivity (Werme et al., 2000), impulsivity (Poulos et al., 1995) or novelty-seeking (e.g., Bardo et al., 1996) dimensions of behavior that may also be genetically determined. A goal of the present experiment was to determine whether or not access to a running-wheel interfered with cocaine-reinforced behavior in randomly selected outbred male and female Wistar rats.

Sex and hormonal status are factors that are increasingly being revealed as important determinants of drug abuse (Lynch et al., 2001, 2002). For example, female animals self-administer more alcohol (Almeida et al., 1998), caffeine (Heppner et al., 1986), cocaine (Carroll et al., 2002; Lynch and Carroll, 1999), fentanyl (Klein et al., 1997; Klein, 2001), heroin (Carroll et al., 2001a, 2002), morphine (Alexander et al., 1978), nicotine (Klein, 2001) and phencyclidine (Carroll et al., 2000) than males. However, there are studies that have found no sex differences in cocaine (Bowen et al., 2001; Haney et al., 1995; Lynch et al., 2000; Roberts et al., 1989), heroin (Stewart et al., 1996) and nicotine (Donny et al., 2000) self-administration. The sex differences that have been reported occur in all phases of addiction: acquisition, maintenance and reinstatement (Lynch et al., 2001), and recent evidence indicates that elevated drug intake in females during acquisition (Lynch et al., 2001; Roth et al., 2002) and maintenance (Lynch et al., 2000) of drug self-administration is due to higher levels of estrogen. Initial results also suggest that there are sex differences in the effects of medications such that female rats (Campbell et al., 2002; Carroll et al., 2001a) and rhesus monkeys (Cosgrove and Carroll, 2002a) show a greater suppression in drug self-administration than males. Thus, it was a goal of the present study to extend the investigation of sex differences to a nondrug alternative reinforcer form of treatment and to determine whether cocaine self-administration was differentially affected by wheel-running in female vs. male rats.

The purpose of the present experiment was to test the hypothesis that like preferred foods, a nonconsummatory event, access to a running-wheel, would reduce intravenous drug self-administration. It was also expected that there would be a reciprocal reinforcer interaction, and cocaine-self-administration would reduce wheel-running. Since previous work indicates there are sex differences in the rate of drug self-administration in rats (Lynch et al., 2001), and initial reports indicate potential sex differences in treatment effects (Campbell et al., 2002; Carroll et al., 2001a,b; Cosgrove and Carroll, 2002a,b), female and male rats were also compared. The present experiment extends previous work by others (Kanarek et al., 1995; McMillan et al., 1995) to a within-subjects design, to female rats and to the intravenous self-administration of cocaine using operant methods. Previous animal work concerning nondrug alternative reinforcers as a potential treatment for drug abuse involved foods or sweetened liquids. In terms of generalizing results to human treatment approaches, it is important to establish models with nonconsummatory incentives.

2. Methods

2.1. Subjects

Nine male rats weighing a mean (±S.E.M.) of 405.11 (±19.13) g and eight female rats weighing a mean of 298.3 (±12.6) g at the start of the experiment were used as subjects (Harlan Sprague–Dawley, Madison, WI). Prior to the experiment, rats were housed individually for at least 5 days in rectangular plastic home cages where they had free access to food and water. Subsequently, the rats were moved to individual operant chambers where they resided for the remainder of the experiment. During this time, food rations were limited to 20 g/day for males and 16 g for females,

amounts that had been previously determined to maintain them at 85% of the free-feeding body weights of age-matched controls (Lynch and Carroll, 1999). Water was freely available throughout the experiment. The rooms in which the rats and the operant chambers were housed were controlled for temperature (24 °C) and humidity. The room lights were on a 12-h light/dark cycle with the lights on from 7 a.m. to 7 p.m., and the rats had a low level of constant illumination in their cage. These lighting conditions resulted in free-running rhythms and stable behavioral baselines. Use of animals for this protocol was approved by the University of Minnesota Institutional Animal Care and Use Committee (Protocol No. 9904A00343). Laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care, and recommended principles of laboratory animal care were followed (National Research Council, 1996).

2.2. Apparatus

The intravenous self-administration chambers were octagonally shaped with alternating stainless-steel and Plexiglas walls. On the stainless steel walls, a drinking bottle, recessed food jar and two response levers (Coulbourn Instruments, Allentown, NJ, USA) were mounted. Three colored stimulus LED lights (red, yellow and green) were located above each lever, which were located on either side of a Plexiglas panel, and opposite the entrance to the chamber. There was a constantly illuminated low-level white house light (4.6 W) mounted at the top of the chamber. Between the left lever and the entrance to the chamber, there was an open space where a stainless-steel panel had been removed, and this allowed access, by an 8-cm step up to a Wahmann (Baltimore, MD) running wheel, which was mounted along the side of the self-administration chamber. The two pieces of apparatus functioned independently, but they were adjoining forming a two-compartment operant chamber, which was housed in a custom-made Melamine covered wooden enclosure. The enclosure was ventilated by an exhaust fan mounted on the outside. The wheel measured $34 \times 14 \times 35$ cm ($l \times w \times h$). The elevation of the wheel allowed the rat to run freely in the running wheel, while the rat remained at the appropriate diameter from a swivel mounted on top of the intravenous chamber to be connected to the infusion tether. The necessity of maintaining a small space between the running-wheel and the self-administration chamber to allow the rat and the wheel to move freely was technically challenging, especially in the case of the much smaller and often more active female rats that were occasionally able to escape to the interior of the sound attenuating chamber. Thus, it was possible to obtain complete data on only six females. Wheel revolutions were counted by a magnetic sensor and sent as a digital signal to the computer-control system. The rats' infusion tubing was covered by a spring-covered cannula (C313CS Plastics One, Roanoke, VA) that was attached to a swivel (050-0022, Alice King Chatham, Hawthorne, CA). The swivel was connected via Tygon tubing (1.52 mm o.d., 0.51 mm i.d.; Fisher Scientific, Springfield, NJ) to an infusion pump that was mounted outside the wooden enclosure. The indwelling cannula originating in the jugular vein of the rat was directed subcutaneously through a small hole over the scapulae to the spring-covered cannula by an attachment (C3236, Plastics One) that was embedded in the center of a soft plastic covance-infusion harness (CIH95; Instech Laboratories, Plymouth Meeting, PA). The experiment was controlled and data were recorded by an IBM-compatible computer with Med-PC interfacing (Med Associates, St. Albans, VT).

2.3. Drugs

Cocaine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC). It was mixed with sterile saline and refrigerated, and it was added to the 500-ml pump reservoirs at room temperature. Reservoirs were located outside each test chamber, and they were covered with aluminum foil. Cocaine infusions (0.2 mg/kg) were delivered at a rate of 0.125 ml/s, and the infusion duration was 1 s/100 g of body weight. Infusion durations ranged from 3.9 to 4.5 s for males and 2.9 to 3.2 s for females, and volumes ranged from 0.487 to 0.563 ml for males and 0.363 to 0.4 ml for females. Infusion volumes (ml), dose (mg) and times (s) were proportional to body weights to account for males being larger than females of the same age. Thus, males and females received identical doses defined as (mg/kg).

2.4. Procedure

Rats had access to the running wheel alone, intravenous cocaine alone, or concurrent wheel and cocaine during the daily 6-h sessions beginning at 0900 h. Between 0800 and 0900 h, food and water intakes for each subject from the preceding day were measured and recorded, water bottles were refilled and chambers were cleaned. Rats were fed daily after session at 1500 h. Once every 7 days, catheter patency was tested by administering sodium methohexital (5 mg/kg iv). An immediate loss of the righting reflex following the injection indicated that the catheter was patent. Rats were also weighed at this time, and the infusion duration was adjusted by reprogramming the computer to reflect any changes in body weight.

Table 1 summarizes the experimental design. In the first phase rats were given access to the running wheel alone for at least 14 consecutive daily sessions until wheel rotations stabilized. Stability was defined as no increasing or decreasing trend in revolutions over 5 consecutive days. Rats were then anesthetized with a combination of ketamine (90 mg/kg) and pentobarbital (10 mg/kg). A silicon cannula was inserted into the right jugular vein according to methods previously described (Carroll and Boe, 1982; Lynch et al., 2000). The free tip of the catheter was led subcutaneously to an incision

Table 1
Experimental procedure

Phases	Duration
Wheel-only	14 days stability period
Surgery	3 days recovery
Cocaine-only	5 days
Wheel + cocaine	5 days
Cocaine-only	5 days
Wheel-only	5 days

placed 1 cm caudal to the scapulae and then to an external harness (Instech) and connected to a swivel at the top of the cage. Rats were allowed 3 days to recover from surgery.

The second phase of the experiment consisted of intravenous cocaine self-administration. Rats were allowed access to cocaine infusions under a fixed-ratio 1 (FR 1) schedule during the daily 6-h sessions. Specifically, one response on the active lever resulted in one infusion of cocaine, and this schedule remained constant throughout the study. Running in the wheel was prevented by latching the wheel to lock it in a still position during this phase of the experiment. The rats could enter the wheel, but it did not turn. To initiate responding for cocaine, rats were given two experimenter-delivered priming infusions for several days at the beginning of the session until consistent lever-pressing leading to cocaine infusions occurred. The criterion for acquisition of cocaine self-administration consisted of a mean of 100 cocaine infusions over 5 consecutive sessions. This criterion was based on previous research on the acquisition of cocaine self-administration (Campbell and Carroll, 2000; Lynch and Carroll, 1999; Lynch et al., 2001).

In the third phase of the study, rats were given concurrent access to cocaine and the running wheel during sessions for at least 10 days or until behavior stabilized. In the fourth phase of the experiment, the wheel was once again locked in a still position, and rats only had access to cocaine to determine whether responding for cocaine would return to baseline levels. The wheel + cocaine phase was subsequently reinstated for 5 days. During the fifth phase of the study, rats were given access only to the running wheel to determine whether running wheel activity would return to baseline levels. Due to the length of the experiment and the difficulty of keeping the cannulas patent for a long duration and technical difficulties associated with wheel-running in tethered rats, only three rats (two males and one female) completed this last phase of the study. During this phase, the swivel and harness remained attached to the rats to determine whether they would affect the rats' ability to run in the wheel compared to the baseline wheel-only condition that occurred before the tethers were attached.

2.5. Data analysis

Dependent measures were mean (±S.E.M.) number of wheel rotations during the last 5 sessions and mean (±S.E.M.) number of cocaine infusions during the last 5 self-administration sessions. Sex was the independent variable. One-tailed, Bonferroni-corrected t tests were used to compare differences between and within groups. Values of $P < .05$ were considered to be statistically significant. Data analyses was performed using the GB-Stat School Pak (Dynamic Microsystems, Silver Spring, MD).

3. Results

In general, both male and female, rats' food and water intakes did not vary as a function of the phase of the experiment or the presence or absence of cocaine self-administration and/or wheel running. The limited amounts of food that were provided (16 and 20 g, respectively) were consistently consumed in both females and males.

Fig. 1 shows the number of cocaine infusions (±S.E.M.) during the initial cocaine-only phase, the cocaine + wheel phase and the subsequent cocaine-only phase for both female and male rats. Under cocaine-only conditions, there was no significant difference in the number of cocaine infusions between males and females or from the first cocaine-only condition to the second. Without access to wheel-running, the number of cocaine infusions during the 6-h session for both males and females was approximately 180 or 30 infusions per hour at the 0.2 mg/kg dose. In females, the left side of Fig. 1 shows that the number of cocaine infusions was significantly reduced to a mean of 55.5 or less than 10 per hour. Thus, there was a 70.6% reduction in infusions when there was concurrent access to

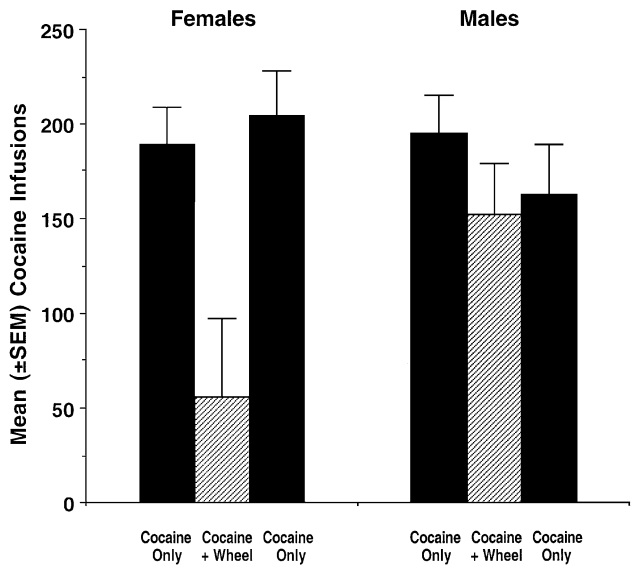

Fig. 1. Mean (±S.E.M.) cocaine (0.2 mg/kg) infusions are presented for females (left bars) and males (right bars) during the sequential cocaine-only, wheel + cocaine and cocaine-only phases, which are indicated by solid, striped and solid bars, respectively. Each bar represents a mean of six (females) or nine (males) rats over the last 5 days when behavior had stabilized during each phase.

the running wheel ($t = 3.34$, $df = 5$, $P < .05$). However, in males, while infusions were decreased slightly (21.9%) to a mean of 152 during concurrent access to the running wheel, there was no statistically significant reduction. In addition, the female rats showed a more consistent effect, with 5 out of 6 reducing infusions during the wheel + cocaine condition, while only 6 of the 9 males showed a reduction. Thus, under conditions of food restriction and a relatively low dose of cocaine (0.2 mg/kg), concurrent access to wheel-running was effective at reducing cocaine self-administration in female but not male rats.

Fig. 2 shows the number of wheel revolutions (± S.E.M.) during the initial wheel-only phase, the wheel + cocaine phase and, for one female and two male rats, the second wheel-only phase. The subsequent wheel-only condition was conducted in only 3 rats because technical difficulties associated with maintaining catheter patency and equipment problems accumulated after completing several phases of the experiment. These results indicate that baseline wheel-only behavior was reinstated the second time the rats had access to the wheel alone, and neither previous cocaine exposure nor having the tether connected affected the number of revolutions. Fig. 2 also indicates that the number of wheel revolutions did not differ between females and males under any of the three conditions. In both males and females, the number of wheel revolutions during the first wheel-only condition was approximately 2000; however, the number of revolutions was reduced to approximately 750 when cocaine self-administration was concurrently available. The reduction in

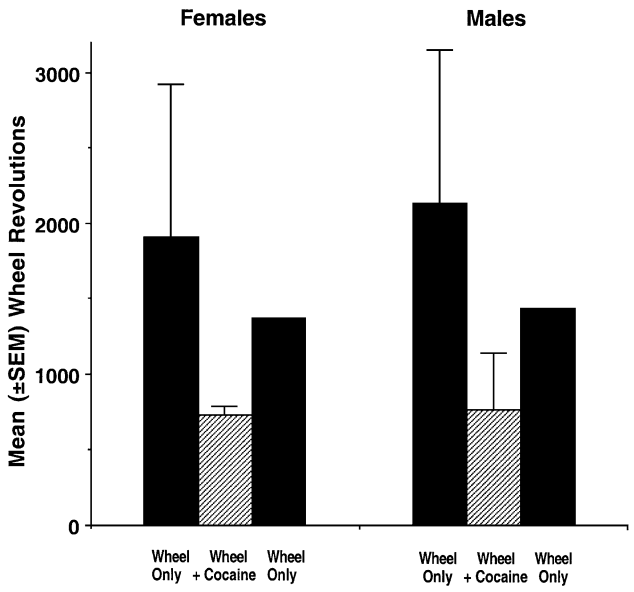

Fig. 2. Mean (± S.E.M.) wheel revolutions are presented for females (left bars) and males (right bars) during the sequential wheel-only, wheel + cocaine and wheel-only phases, which are indicated by solid, striped and solid bars, respectively. The first two bars in each group represent a mean of six (females) or nine (males) rats over the last 5 days when behavior had stabilized during each phase. The last bar represents one female (left) and two male (right) rats.

Table 2
Mean wheel revolutions (5 days)

Rat number	Wheel-only	Wheel + cocaine	Wheel-only
Females			
#3325	1275.4	312.4	1376.8
Males			
#3411	1922.2	151.4	2018.8
#3661	731	175.2	856

mean wheel revolutions was 61.5% in females and 63.7% in males, but due to the high variability in the first wheel-only condition, this effect was not statistically significant. When the male and female wheel-revolution data were combined, as there were no sex differences, there was a significant reduction in wheel-running during concurrent access to cocaine self-administration ($t = 1.96$, $df = 14$, $P < .05$). Thus, access to intravenous cocaine significantly suppressed wheel-running when a larger group of rats ($N = 15$) was compared. A final wheel-only phase was conducted in only a limited number of rats due to a limited number of multi-purpose chambers and to technical problems encountered when measuring wheel-running in tethered rats. Thus, while in these 3 rats, the number of wheel revolutions appeared to return to the baseline approaching 2000, it was not possible to conduct statistical analyses with this second wheel-only condition (Table 2).

4. Discussion

Access to a running wheel in a compartment adjoining the drug self-administration chamber served as an alternative reinforcer that reduced intravenous cocaine self-administration, and the effect was more pronounced in females than in males. The present results extend previous findings with oral intake of amphetamine (Kanarek et al., 1995) and ethanol (McMillan et al., 1995) to intravenous cocaine self-administration and operant responding that was reinforced by intravenous cocaine self-administration. This model of substituting natural reinforcement (exercise) for drug-taking behavior has the advantage of using an alternative behavior that does not involve consumption of other substances (which may become excessive). Wheel-running, unlike general exploratory behavior, does not habituate, and it may be a useful tool for understanding factors that increase or decrease drug abuse, such as sensitization, or substitution of nondrug incentives, respectively. These results are comparable to those reported previously for food (Carroll, 1996; Carroll et al., 2001a) and sweetened liquids (Carroll et al., 2001b, 2002), in animals, and for incentive vouchers (Silverman et al., 1996a,b, 1998) and money (Heishman et al., 2000) in human subjects. When cocaine was available alone after the combined wheel + cocaine access, infusions returned to the prewheel baselines in both males and females. Thus, the suppressant effect of wheel-running on cocaine self-administration was transient, and it did not

endure after concurrent access to the alternative activity was removed. These results suggest that designing a strategy for subject-initiated and -maintained nondrug alternative reinforcement might be necessary for maintaining reductions in drug consumptions.

In addition to the greater percent reduction in cocaine self-administration during wheel-running, compared to cocaine-only (21.9% and 70.6% in males and females, respectively), the present results also indicated that wheel-running was reduced during cocaine access in males and females by 63.7% and 61.5%, respectively, from a baseline of wheel-only. Due to the high intersubject variability, this reduction was statistically significant only when data from male and female rats were combined. Thus, in females, there was a symmetrical substitution of the drug (cocaine) and nondrug (wheel-running) reinforcers. In males, the effect was asymmetrical. Wheel running was reduced more by cocaine access than cocaine self-administration was reduced by wheel access. Due to the length of this within-subjects protocol, and the complexity of keeping cannulae patent while allowing free-moving access to running-wheel and self-administration chambers, only 3 rats completed the final wheel-only condition. Wheel-running during this final condition returned to levels that were very close to the wheel-only baseline after wheel + cocaine access in all of these rats. Thus, there were no prolonged behavioral reductions that could be attributed to irreversible changes in behavior or to other factors such as cocaine withdrawal.

Another explanation of the reduction in cocaine self-administration (in females) during wheel access and the reduction in wheel-running during cocaine access compared to baselines of access to either reinforcer alone is that the two behaviors are mutually exclusive, and time spent doing one activity reduces time left for the other. Since an analysis of the time course of cocaine- and wheel-maintained behavior over the 6-h session revealed that the rats spent more than half of their time doing neither, this explanation is not well-supported. Furthermore, the males were able to self-administer nearly the same amounts of cocaine whether there was wheel access or not. The males' rate of wheel-running was slower than the females; thus, they did not have more time for cocaine self-administration because they ran faster. Of the three potential explanations for the present results, direct effects, time limitations and reinforcer substitution, the latter is the most plausible. This also agrees with an initial study of the effect of a concurrent alternative nondrug reinforcer, saccharin on phencyclidine (PCP) self-administration (Carroll, 1985). Access to saccharin reduced PCP self-administration, but saccharin self-administration persisted after drug intake had stopped, and food and water intake was not affected. Thus, direct effects of this drug did not explain the results, as saccharin intake continued.

The effect of cocaine on wheel-running may have been due to a general suppression in behavior due to the direct effects of the drug or to an interaction between the rewarding effects of these activities. A general behavioral suppression is unlikely, since there was no effect on food or water intake. A well-controlled test for direct effects would have involved a yoked-control group that had access to the wheel but had cocaine administered noncontingently at the same dose and temporal pattern as the experimental group self-administered the drug.

The effect of wheel-running activity on drug self-administration may also be due to a generalized effect of novelty, if novelty is construed in the relative sense. While the rats had initial exposure to wheel-only for at least 2 weeks, the activity was still relatively novel within the context of several months of being housed in a standard rat cage or operant chamber. Others have shown that exposure to novel stimuli reduces amphetamine self-administration (Bardo et al., 2001; Klebauer et al., 2001). Novel stimuli and food may activate the mesolimbic dopamine system similar to the effects of drugs of abuse on mesolimbic dopamine pathways. In rats, a novelty-induced place preference was blocked by dopamine antagonists (Bardo et al., 1989) and by nucleus accumbens lesions (Pierce et al., 1990). In human imaging studies, dopamine was released in the ventral striatum while volunteers played a novel video game (Koepp et al., 1998).

The current finding that cocaine reduced wheel-running is consistent with other reports that drugs such as amphetamine (Williams and White, 1984; Bradbury et al., 1987; Geary et al., 1992), methamphetamine (Masuda et al., 1996) and morphine (Silva and Heyman, 2001) decrease wheel-running. In contrast, others have shown that amphetamine (Evans and Vaccarino, 1986; Bradbury et al., 1987), cocaine (Barron et al., 1994; Ito et al., 1997) and methamphetamine (Honma et al., 1991; Uchihashi et al., 1994; Kosobud et al., 1998) increase wheel running. These discrepancies may be due to the experimental context, specifically whether the drug precedes wheel access, as is the case when drugs increase wheel-running, or whether drug and wheel-running are concurrently available (present study). Another factor is whether or not the drugs are in a context in which they are functioning as reinforcers. Finally, dose of the drug influences wheel running. Specifically, lower doses of d-amphetamine reduced, and higher doses increased locomotor activity in mice (Bradbury et al., 1987; Hussey et al., 1983).

The enhanced treatment effect of wheel-running on cocaine self-administration found in the present study for female over male rats is consistent with recent reports of more pronounced medication effects in female (vs. male) animals. For example, baclofen, a gamma amino butyric acid ($GABA_B$) agonist, reduced the acquisition of cocaine self-administration to a greater extent in female than in male rats (Campbell et al., 2002). Similarly, ketoconazole, which suppresses corticosterone synthesis, reduced heroin self-administration more in females than in males, but only under "stressful" conditions such as food restriction (Carroll et al., 2001b). This general sex difference in treatment has been reported in the use of bremazocine (a kappa opioid receptor agonist) and saccharin (Cosgrove and Carroll, 2002a,b) on

phencyclidine self-administration in rhesus monkeys, and there are clinical data in humans suggesting that women are more responsive to treatment than men (Gil-Rivas et al., 1996; Kosten et al., 1993; Pettinati et al., 1997; Weiss et al., 1997). Taken together, the present results and previous literature indicate that females, in general, may be more treatment receptive than males. However, these initial results are the first to compare the effects of nondrug alternative reinforcement in males and females, and further work with animals and humans is needed to substantiate these findings. In contrast to the sex differences in treatment, no sex differences were found in baseline rates of cocaine self-administration or wheel-running. Previous reports have indicated that females exceed males in cocaine self-administration (Lynch et al., 2000); however, sex differences are less likely to emerge under conditions of food-restriction and the maintenance (vs. acquisition) phase of drug self-administration, as in the case of the present experiments, these are conditions that may produce a ceiling effect.

The present results with wheel-running indicate that the voluntary wheel-running model in rats and possibly voluntary exercise in humans (e.g., Ussher et al., 2000, 2001) might be used as a substitutable natural reward to reduce drug abuse. While this type of nondrug reward, as well as the preferred dietary substances that have been used previously (e.g., Carroll, 1996), suppress ongoing drug taking behavior when they are concurrently available, it should be recognized that the subjects' response to the nondrug reward when it is presented alone can also be used as a predictor of drug-taking potential. For example, rats that are selected for an excessive amount of saccharin or glucose intake (Carroll et al., 2002; Dess et al., 1998; Gahtan et al., 1996; Gosnell, 2000; Gosnell and Krahn, 1992; Kampov-Polevoy et al., 1995a,b, 1999), locomotor activity (Mantsch et al., 2001; Piazza et al., 1989), impulsivity (Poulos et al., 1995), compulsivity (Werme et al., 2000) or novelty-seeking (Bardo et al., 1996) show higher rates of drug self-administration than their counterparts with lower scores on these measures. In contrast, the same stimuli; activity (Kanarek et al., 1995; McMillan et al., 1995; present results), novelty (Bardo et al., 2001), saccharin (Campbell et al., 1998; Carroll et. al., 2002) or glucose (Carroll et al., 1989; West et al., 1999) prevent or reduce drug self-administration. The positive results of reducing cocaine self-administration by offering access to wheel-running found in the present study will be extended to identify variables that are responsible for the effect. For example, would prior exposure to wheel-running sensitize rats to the subsequent reinforcing effects of cocaine? Is binge cocaine use that results from escalation of cocaine intake more resistant to the suppressant effects of running-wheel access than regulated use? How does the wheel treatment effect vary as a function of phase of the estrous cycle? Experiments are currently under way to determine whether rats that are selected for high wheel-running are more vulnerable to acquire and maintain higher levels of drug self-administration than those selected for lower scores on these measures. This approach will serve as a means of screening animals and ultimately humans for behavioral characteristics that predict drug abuse disorders.

Acknowledgments

The authors would like to thank Beth Drewitz, Christina Gremel and Annemarie Loth for their technical assistance, and Erin Larson, Andrew Morgan and Megan Roth for their helpful comments on the manuscript. Portions of this paper were presented at the meeting of the College on Problems of Drug Dependence, Scottsdale, AZ on June 2001. This research was supported by grants R37 DA03240 (MEC), F31 AA005575 (KPC) and a donation by Aaron Arel.

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