Pharmacology, Biochemistry and Behavior 150–151 (2016) 94–99

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Acute bouts of wheel running decrease cocaine self-administration: Influence of exercise output

Mark A. Smith *, Gaylen E. Fronk, Huailin Zhang, Charlotte P. Magee, Andrea M. Robinson

Department of Psychology, Program in Neuroscience, Davidson College, Davidson, NC 28035, USA

ARTICLE INFO

Article history:
Received 14 August 2016
Received in revised form 9 September 2016
Accepted 4 October 2016
Available online 05 October 2016

Keywords:
Cocaine
Exercise
Rat
Self-administration
Wheel

ABSTRACT

Exercise is associated with lower rates of drug use in human populations and decreases drug self-administration in laboratory animals. Most of the existing literature examining the link between exercise and drug use has focused on chronic, long-term exercise, and very few studies have examined the link between exercise output (i.e., amount of exercise) and drug self-administration. The purpose of this study was to examine the effects of acute bouts of exercise on cocaine self-administration, and to determine whether these effects were dependent on exercise output and the time interval between exercise and drug self-administration. Female rats were trained to run in automated running wheels, implanted with intravenous catheters, and allowed to self-administer cocaine on a fixed ratio (FR1) schedule of reinforcement. Immediately prior to each test session, subjects engaged in acute bouts of exercise in which they ran for 0, 30, or 60 min at 12 m/min. Acute bouts of exercise before test sessions decreased cocaine self-administration in an output-dependent manner, with the greatest reduction in cocaine intake observed in the 60-min exercise condition. Exercise did not reduce cocaine self-administration when wheel running and test sessions were separated by 12 h, and exercise did not reduce responding maintained by food or responding during a saline substitution test. These data indicate that acute bouts of exercise decrease cocaine self-administration in a time- and output-dependent manner. These results also add to a growing body of literature suggesting that physical activity may be an effective component of drug abuse treatment programs.

1. Introduction

Individuals who engage in exercise-related activities over the course of treatment for substance use disorders have better outcomes relative to individuals who do not engage in exercise-related activities (Brown et al., 2010; Weinstock et al., 2008). Preclinical studies have consistently shown that rats given free access to exercise wheels in their home cage self-administer less cocaine, methamphetamine, and other psychomotor stimulants than sedentary control rats (Aarde et al., 2015; Miller et al., 2012; Smith et al., 2008, 2011, 2012). Most preclinical studies reporting positive effects of wheel running on drug self-administration have used exercise protocols that employed long-term access to running wheels for 6 weeks or longer (e.g., Lacy et al., 2014; Smith et al., 2008, 2011, 2012); however, the positive effects of wheel running on drug self-administration are observed even in the absence of extended access (Smith and Witte, 2012) and may be observed in as little as 22 h (Aarde et al., 2015).

Acute exercise, defined as a single, short-term bout of exercise, produces positive effects on several psychological measures that influence drug self-administration. For instance, acute bouts of exercise decrease measures of depression and anxiety (Dunn et al., 2001; Fritz and O'Connor, 2016) and increase measures of self-esteem and wellbeing (Fox, 1999). Moreover, acute bouts of exercise reduce measures of impulsivity (Wang et al., 2016) and increase measures of cognitive functioning (Kamijo et al., 2009; Nanda et al., 2013; Weng et al., 2015). Acute exercise reduces the symptoms associated with nicotine withdrawal (Abrantes et al., 2014; Bock et al., 1999; Prapavessis et al., 2014; Williams et al., 2011) and reduces craving for nicotine and methamphetamine (Elibero et al., 2011; Haasova et al., 2013; Wang et al., 2016); however, the effects of acute exercise on measures of drug intake have not been examined.

The effects of an acute bout of exercise on psychological processes related to drug use are dependent on exercise output. For instance, light and moderate exercise decrease methamphetamine craving relative to both vigorous exercise and a sedentary control condition (Wang et al., 2016). Similarly, exercise output also determines the effects of acute exercise on measures of mood (Steptoe and Cox, 1988; Tate and Petruzzello, 1995), executive control (Labelle et al., 2013), and cognitive functioning (Loprinzi and Kane, 2015; McMorris and Hale, 2012; Tomporowski,

* Corresponding author at: Department of Psychology, Davidson College, Box 7037, Davidson, NC 28035-7037, USA.
E-mail address: masmith@davidson.edu (M.A. Smith).

http://dx.doi.org/10.1016/j.pbb.2016.10.001
0091-3057/

2003). Preclinical studies examining the effects of exercise on measures of drug intake have typically manipulated access to running wheels rather than exercise output per se. Consequently, the effects of exercise output on drug self-administration are not known.

The purpose of the present study was to examine the effects of acute bouts of exercise on cocaine self-administration and to determine whether these effects are dependent on exercise output. To this end, rats were trained in a forced-running procedure using automated running wheels rotating at a speed of 12 m/min. Forced running rather than voluntary running was selected so that exercise output could be controlled as an experimental manipulation. All subjects ran in the wheels for 0 min (sedentary control), 30 min (short duration), or 60 min (long duration) immediately prior to intravenous drug self-administration sessions. Our primary hypothesis was that acute exercise would decrease cocaine self-administration in an output-dependent (i.e., duration-dependent) manner.

2. Method

2.1. Animals

Female, Long-Evans rats ($n = 16$) were obtained on postnatal day 42 (PND 42) from Charles River Laboratories (Raleigh, NC). Rats were housed individually in transparent polycarbonate cages that permitted no exercise beyond normal cage ambulation. All rats were housed in a temperature- and humidity-controlled colony room maintained on a 12-hour light/dark cycle (lights on: 0500). Except during periods of food-maintained responding, food was freely available in the home cage; water was continuously available in the home cage for the duration of the study. Estrous phases were allowed to cycle normally and not monitored. All subjects were maintained in accordance with the Institutional Animal Care and Use Committee of Davidson College and the *Guide for the Care and Use of Laboratory Animals* (Institute for Laboratory Animal Resources, 2011).

2.2. Apparatus

Self-administration training and testing took place in aluminum and polycarbonate operant conditioning chambers (interior dimensions: 31 cm × 24 cm × 21 cm) obtained from Med Associates, Inc. (St. Albans, VT). Each chamber was equipped with a house light, an audio speaker, two response levers, two stimulus lights above the levers, and a food receptacle located between the two levers. A food pellet dispenser was located behind the forward wall and an infusion pump was mounted outside the chamber. Drug infusions were delivered via Tygon tubing protected by a stainless-steel spring and attached to a counter-balanced swivel at the top of the chamber. All chambers were housed in larger, sound-attenuating cabinets with an exhaust fan to circulate air and to mask extraneous noise. Experimental procedures were programmed and data were collected using software and interfacing from Med Associates, Inc.

Wheel running was experimentally controlled via automated running wheels. The wheels and motorized wheel bed were obtained from Lafayette Instrument Company (Lafayette, IN). The wheels measured 34.0 cm in diameter and 11.2 cm in width. Each wheel had polycarbonate sides with 82 aluminum rungs (4.8 mm in diameter) spaced 13.4 mm apart. The running surface of the wheels was lined with low-density polyethylene mesh to prevent tails from getting pinched while running. Six wheels could rotate simultaneously when placed in the wheel bed (exterior dimensions: 130 cm × 46 cm × 43 cm). The speed and duration of wheel rotation were programmed via a handheld LCD interface.

2.3. Exercise training

Three days after arrival, rats began daily training on the running wheels. On the first day of exposure, rats ran at a speed of 3 m/min for 15 min. The speed increased by 1 m/min and the duration increased by 5 min each day until the terminal speed of 12 m/min and duration of 60 min was reached after 10 days. Rats ran at this speed and duration for three consecutive days before catheter surgery and the commencement of self-administration training.

2.4. Lever-press training

One week after arrival and during the second week of exercise training, rats were restricted to 85% of the free-feeding body weight and trained to lever press using food reinforcement. During these sessions, responding was reinforced with a single 45 mg food pellet on a fixed ratio (FR1) schedule of food presentation. Each session continued until 40 reinforcers were delivered or 2 h elapsed, whichever occurred first. Training continued in this manner until a rat received the maximum number of reinforcers in each of four training sessions. All rats met this criterion within 7 days.

2.5. Surgery

Three weeks after arrival and one day following the completion of exercise training, rats were anesthetized with a combination of ketamine (100 mg/kg, ip) and xylazine (15 mg/kg, ip) and surgically implanted with intravenous catheters into the right jugular vein. Catheters exited the body on the dorsal surface of the scapulae. Ketoprofen (5.0 mg/kg, sc) was given immediately after surgery and the following morning as a postoperative analgesic. A solution of heparinized saline and ticarcillin (20 mg/kg, iv) was infused through the catheter daily to maintain patency and prevent infection, respectively. After 7 days, ticarcillin administration was discontinued and only heparinized saline was used to maintain catheter patency.

2.6. Self-administration training

Self-administration training commenced 4 days following surgery. Immediately prior to each training session, rats were placed on the automated running wheels at 12 m/min for 30 min. Rats were then moved directly to the operant conditioning chambers and connected to the infusion pump via the Tygon tubing. All sessions began with illumination of the house light, illumination of the stimulus light above one (active) response lever, and a non-contingent infusion of cocaine (Sigma Chemical Company, St. Louis, MO). Each response on the active response lever produced an infusion of cocaine (0.5 mg/kg/infusion) on a FR1 schedule of reinforcement. Coincident with the infusion, a tone was sounded for 5 s and the stimulus light above the response lever turned off for 20 s to signal a timeout period in which cocaine was not available. After 20 s, the light above the lever was re-illuminated and cocaine was available on the FR1 schedule of reinforcement. Responses on the second (inactive) response lever were recorded but had no programmed consequences. Training continued in this manner for 5 consecutive days.

2.7. Self-administration testing

Following 5 days of self-administration training, behavioral testing commenced. The exercise manipulation was performed at the beginning of the dark phase of the light/dark cycle (1700), immediately prior to each test session. Using a within-subjects design, each rat was exposed to one of the following three exercise conditions immediately before each test session: (1) a sedentary control condition, (2) a short-duration condition, or (3) a long-duration condition. In the sedentary condition, rats were taken to the testing room and placed in clean polycarbonate cages for 60 min. In the short-duration condition, rats were taken to the testing room, placed in clean polycarbonate cages for 30 min and then placed in the automated running wheels rotating at 12 m/min for an additional 30 min. In the long-duration condition, rats were taken to the testing room and placed in the automated