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Access to a running wheel inhibits the acquisition of cocaine self-administration

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ABSTRACT

Physical activity decreases cocaine self-administration in laboratory animals and is associated with positive outcomes in substance abuse treatment programs; however, less is known about its efficacy in preventing the establishment of regular patterns of substance use in drug-naive individuals. The purpose of the present study was to examine the effects of access to a running wheel on the acquisition of cocaine self-administration in experimentally naive rats. Male, Long–Evans rats were obtained at weaning and assigned to sedentary (no wheel) or exercising (access to wheel) conditions immediately upon arrival. After six weeks, rats were surgically implanted with intravenous catheters and placed in operant conditioning chambers for 2 h/day for 15 consecutive days. Each session began with a noncontingent priming infusion of cocaine, followed by a free-operant period in which each response on the active lever produced an infusion of cocaine on a fixed ratio (FR1) schedule of reinforcement. For days 1–5, responding was reinforced with 0.25 mg/kg/infusion cocaine; for days 6–15, responding was reinforced with 0.75 mg/kg/infusion cocaine. In addition, all rats were calorically restricted during days 11–15 to 85% to 95% of their free-feeding body weight. Compared to sedentary rats, exercising rats acquired cocaine self-administration at a significantly slower rate and emitted significantly fewer active lever presses during the 15 days of behavioral testing. These data indicate that access to a running wheel inhibits the acquisition of cocaine self-administration, and that physical activity may be an effective intervention in substance abuse prevention programs.

1. Introduction

A rapid transition from initial drug exposure to regular patterns of drug use is considered an important prognosticator of whether an individual will later develop problems with substance abuse and dependence (U.S. Congress, Office of Technology Assessment, 1994). Consequently, one of the goals of substance abuse prevention programs is to discourage the development of regular patterns of drug use in at-risk populations. The acquisition of regular patterns of drug intake after initial drug exposure can be modeled in the laboratory by exposing an animal to noncontingent drug infusions and then permitting the animal to self-administer that drug in free-operant test sessions. Factors that influence the acquisition of drug self-administration in the laboratory are often identical to the factors that influence the likelihood an individual will develop problems with substance abuse and dependence. For instance, social isolation (Kosten et al., 2000), stress (Tidey and Miczek, 1997), and previous drug exposure (Fletcher et al., 2001) increase the rate of acquisition in laboratory animals and are considered risk factors for developing problems with substance use in humans. Moreover, interventions that decrease the rate of acquisition in laboratory animals, such as access to alternative nondrug reinforcers, decrease the probability that human populations will develop problems with substance use (see review by Campbell and Carroll, 2000). For instance, providing laboratory rats with concurrent access to a palatable drinking solution reduces the acquisition of intravenous cocaine self-administration (Carroll and Lac, 1993), whereas providing adolescents with educational programs and social activities reduces the initiation of alcohol drinking (Perry et al., 1996, 2002).

Physical activity is one intervention that may reduce the likelihood that an individual will transition into regular patterns of drug use. Epidemiological studies report that adolescents who engage in regular physical activity are less likely to use drugs and alcohol (Field et al., 2001; Kirkcaldy et al., 2002; Ströhle et al., 2007; Iannotti et al., 2009) and have fewer risk factors that are associated with the development of substance use disorders (Collingwood et al., 1991, 2000) than their peers who do not engage in regular physical activity. Preclinical studies reveal that physical activity reduces drug self-administration in procedures that model different transitional stages in the development of substance use disorders. For instance, access to a running wheel decreases the maintenance of cocaine-reinforced behavior in animals with well-established self-administration histories (Cosgrove et al., 2002; Smith et al., 2008), and reduces drug-primed (Zlebnik et al., 2010) and cue-induced (Lynch et al., 2010) reinstatement of cocaine-seeking behavior in animals after a period of forced abstinence. The ability of wheel running to influence the acquisition of cocaine self-administration (i.e., the establishment of regular patterns of cocaine self-administration) is not known.

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The purpose of the present study was to examine the effects of access to a running wheel on the acquisition of cocaine self-administration. To this end, sedentary (no wheel) and exercising (access to wheel) rats were implanted with intravenous catheters and allowed to self-administer cocaine in free-operant test sessions. Each session began with a priming infusion of cocaine, followed by a 2-h period in which cocaine was available on a fixed ratio (FR1) schedule of reinforcement. Previous studies report that the rate of acquisition is influenced by both the dose of cocaine used to reinforce behavior (Carroll and Lac, 1997) and the level of caloric restriction at the time of testing (Specker et al., 1994; Campbell and Carroll, 2001). In the present study, acquisition testing advanced through three distinct stages designed to systematically increase the probability that self-administration would be acquired. In phase 1 (days 1–5), responding was reinforced with 0.25 mg/kg/infusion cocaine; in phase 2 (days 6–10), responding was reinforced with 0.75 mg/kg/infusion cocaine; and in phase 3 (days 11–15) responding was reinforced with 0.75 mg/kg/infusion cocaine and animals were calorically restricted to 85% to 95% of their free-feeding body weight. We hypothesized that rates of active lever pressing would increase over the 15-day period, and that access to a running wheel would significantly decrease the rate of acquisition.

2. Material and methods

2.1. Animals and apparatus

Male Long–Evans rats were obtained at 21 days of age from Charles River Laboratories (Raleigh, NC, USA) and assigned randomly to sedentary and exercising conditions immediately upon arrival. Sedentary rats were housed in polycarbonate cages (interior dimensions: $50\times28\times20$ cm) that permitted no physical activity beyond normal cage ambulation. Exercising rats were housed in identical cages but with a running wheel (interior diameter: 35 cm) from Harvard Apparatus (Holliston, MA, USA) affixed to the interior of the cage. Mechanical switches on each wheel recorded the number of revolutions. Cages with locked or inactive wheels were not used for the sedentary control group because rodents climb in locked running wheels (Koteja et al., 1999), potentially compromising the primary experimental manipulation of the study (i.e., physical activity). All rats remained in their respective sedentary and exercising conditions for the duration of the study. During the period of behavioral testing, exercising rats had full access to their running wheels before and after each session. Drinking water was continuously available in the home cages. Food was freely available in the home cages except for the final few days of the study during which the rats were lightly food restricted (see below). Rats were maintained on a 12-h light/dark cycle (lights on: 7:00 a.m.) in a temperature- and humidity controlled vivarium. All subjects were maintained in accordance with the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animals Resources, 1996) and the Institutional Animal Care and Use Committee of Davidson College. A total of 46 rats were assigned to the sedentary and exercising conditions ($n=23$ sedentary; $n=23$ exercising). Rats that lost catheter patency at any point during testing were removed from the study and their data were not included in the statistical analysis. A total of 38 rats completed the study ($n=19$ sedentary; $n=19$ exercising).

All experiments were conducted in polycarbonate and aluminum operant conditioning chambers (interior dimensions: $31\times24\times21$ cm) from Med Associates, Inc. (St Albans, VT, USA). Each chamber was equipped with two response levers on one wall, a white stimulus light located above each lever, and a houselight located on the opposite wall. Drug infusions were delivered from an infusion pump mounted outside the chamber via Tygon tubing protected by a stainless steel spring and attached to a counter-balanced swivel suspended above the chamber. All experimental events were programmed and data were collected with software and interfacing from Med Associates, Inc.

2.2. Procedures

Approximately six weeks after arrival, rats were anesthetized with a combination of ketamine (100 mg/kg, ip) and xylazine (8 mg/kg, ip) and surgically implanted with intravenous catheters into the right jugular vein. Butorphanol (1.0 mg/kg, sc) was given after surgery and the following morning as an analgesic. A solution of heparinized saline and ticarcillin (20 mg/kg, iv) was infused through the catheter daily to prevent infection and maintain catheter patency. After 7 days, ticarcillin was discontinued and only heparinized saline was used to maintain patency. All rats were allowed to recover for 3–4 days prior to the beginning of self-administration testing.

During self-administration tests, rats were removed from their home cages, placed in the operant conditioning chambers, and connected to the infusion pumps via Tygon tubing. Each session began with illumination of the house light, illumination of the white stimulus light above the active lever, and a noncontingent infusion of cocaine. During all sessions, lever presses were reinforced on a fixed ratio (FR1) schedule of reinforcement. On this schedule, responses on the active lever produced an infusion of cocaine, with infusion duration varying between 2.5 and 3.5 s depending on body weight. Coincident with the start of each infusion, the stimulus light above the active lever turned off for 20 s to signal a timeout during which cocaine was not available and responses had no programmed consequences. For all sessions, responses on the inactive lever were recorded but had no programmed consequences. Sessions lasted for 2 h or until 50 infusions were delivered, whichever occurred first. One session was conducted each day for 15 consecutive days.

Behavioral testing advanced through three consecutive five-day phases. During the first phase (days 1–5), each infusion, including the priming infusion, delivered 0.25 mg/kg cocaine. During the second phase (days 6–10), each infusion, including the priming infusion, delivered 0.75 mg/kg cocaine. During the third phase (days 11–15), each infusion delivered 0.75 mg/kg cocaine (the same as the second phase). Also during the third phase, rats were calorically restricted to 85% to 95% of their free-feeding body weight. Food restriction began immediately after the 10th session, and continued until the end of testing. Food restriction was individualized for each rat, and body weight was not allowed to drop greater than 5% in any rat during any 24-h period. The three phases were designed to systematically increase the probability that rats would acquire cocaine self-administration. Progression through the three stages was the same for all rats, regardless of when they acquired cocaine self-administration.

Acquisition was operationally defined as obtaining 12 infusions on each of two consecutive days, with the first of those days marking the date of acquisition. Thus, it was possible for a rat to meet the acquisition criterion on the first day, provided that at least 12 infusions were obtained on both the first and second day of testing. Any rat that obtained 12 infusions for the first time on the 15th day received one additional test day. If that rat obtained at least 12 infusions on the 16th day, then it was considered to have met the acquisition criterion on the 15th day. During the 16th session, all conditions were identical to those present during the 15th session. No rat ever obtained at least 12 infusions on one day of testing without obtaining at least 12 infusions on all subsequent days of testing, the lowest number for which this was true. Consequently, the 12-infusion criterion was able to discriminate between those rats that had acquired cocaine self-administration and those that had not.

2.3. Data analysis

Wheel running (rev/day) and body weight (g) during the first six weeks of the study were analyzed via repeated-measures ANOVA