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Short communication

Wheel running decreases the positive reinforcing effects of heroin

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Abstract:
Background: The purpose of this study was to examine the effects of voluntary wheel running on the positive reinforcing effects of heroin in rats with an established history of drug self-administration.
Methods: Rats were assigned to sedentary (no wheel) and exercise (wheel) conditions and trained to self-administer cocaine under positive reinforcement contingencies. Rats acquiring cocaine self-administration were then tested with various doses of heroin during daily test sessions.
Results: Sedentary rats self-administered more heroin than exercising rats, and this effect was greatest at low and moderate doses of heroin.
Conclusion: These data suggest that voluntary wheel running decreases the positive reinforcing effects of heroin.

Key words:
heroin; physical activity; positive reinforcement; rat; self-administration

Abbreviations: ANOVA – analysis of variance, AUC – area under the curve, FR – fixed ratio

Introduction

Physical activity increases central dopamine concentrations [14], alters the density of dopamine binding proteins [6], and decreases the positive reinforcing effects of cocaine [4, 17]. Physical activity also increases central concentrations of endogenous opioid peptides [2, 8], and produces positive affective states that are mediated by opioid receptors [13]. Long-term physical activity alters the density of opioid binding proteins [5], and decreases sensitivity to exogenously administered opioid agonists [18]. In laboratory rats with no prior history of drug self-administration, forced treadmill running for 90 min/day for 30 consecutive days reduced responding maintained by a moderate dose of morphine [9], suggesting that physical activity may decrease the positive reinforcing effects of opioids in a manner similar to that reported for cocaine. The purpose of the present study was to examine the effects of voluntary wheel running on heroin self-administration in laboratory rats with an established history of drug self-administration.

Materials and Methods

Animals and Materials

Male Long-Evans rats were obtained at weaning (21 days) from Charles River Laboratories (Raleigh, NC,

USA) and randomly assigned to sedentary or exercising conditions. Sedentary rats were housed individually in polycarbonate cages (interior dimensions: 50 × 28 × 20 cm) that permitted no exercise beyond normal cage ambulation; exercising rats were housed in similar cages equipped with running wheels (interior diameter: 35 cm) connected to mechanical switches that recorded each revolution. Cages with locked running wheels were not used for the sedentary control group because rodents climb in locked wheels [11], potentially compromising the principal experimental manipulation of the study (i.e., physical activity). All subjects were kept in a temperature- and humidity-controlled colony room maintained on a 12-h light/dark cycle (lights on: 07:00). Food and drinking water were available in the home cage. All subjects were maintained in accordance with the Institutional Animal Care and Use Committee of Davidson College. Rats that lost catheter patency or failed to acquire the lever press response were removed from the study and their data were not included in the statistical analysis. A total of 35 rats completed all phases of the study (n = 17 sedentary; n = 18 exercising).

All training and testing sessions were conducted in polycarbonate and aluminum operant conditioning chambers (interior dimensions: 31 × 24 × 21 cm) from Med Associates, Inc. (St. Albans, VT, USA). All chambers contained two response levers located on one wall, two white stimulus lights located immediately above the levers, and one house light located on the opposite wall. Drug infusions were delivered from an infusion pump mounted outside the chamber through a Tygon tube protected by a stainless steel spring and attached to a counterbalanced swivel above the chamber. Experimental events were programmed and data were collected through software and interfacing from Med Associates, Inc. The left lever was designated the active lever for all rats.

Diacetylmorphine (heroin) and cocaine HCl were generously supplied by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC, USA).

Procedure

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 according to methods described previously [15]. All rats were allowed to recover for 3–4 days before beginning self-administration training.

Training and testing sessions were conducted during the light phase of the light/dark cycle so as not to interfere with nocturnal running. Each session began with illumination of the house light, illumination of the white stimulus light above the left response lever, and a noncontingent drug infusion. Throughout the session, responses were reinforced on a fixed ratio (FR1) schedule of reinforcement. On this schedule, each response produced a drug infusion, with infusion duration varying between 2.5 and 3.5 s depending on body weight. Coincident with the beginning of each infusion, the stimulus light above the lever turned off for 20 s to signal a timeout period in which the drug was not available and responses had no programmed consequences. All sessions lasted 2 h and no limits were placed on the number of infusions that could be earned, other than those imposed by the session length and post-infusion timeout.

Fifteen training sessions were conducted over 15 consecutive days. Cocaine was used during training because rats acquire cocaine self-administration readily, and because stable patterns of responding are evident within 2–3 days of acquisition. For the first five days of training, responding was reinforced with 0.25 mg/kg/infusion cocaine; for the subsequent 10 days of training, responding was reinforced with 0.75 mg/kg/infusion cocaine. Any rat that failed to acquire cocaine self-administration did not proceed to heroin testing. Data obtained during the training phase of the study were described previously [16].

Self-administration tests with heroin began the day after the final training session with cocaine. In these tests, doses of heroin (0.001, 0.003, 0.01, and 0.03 mg/kg/infusion) and saline were tested in a pseudo-random order across five daily test sessions. Each session began with a priming infusion of the available dose of heroin, followed by a 2-h free operant period. All other conditions were identical to those used during training.

Data analysis

Data from the final cocaine self-administration session and data from the saline substitution test were analyzed *via* independent-samples *t*-tests using group (sedentary *vs.* exercise) as the factor. Data from the heroin self-administration sessions were analyzed *via* two-way, mixed-factor ANOVA, with group serving as a between-subjects factor and dose serving as the repeated measure. Area under the curve (AUC) estimates were derived from the heroin dose-effect

curves and analyzed *via* an independent-samples *t*-test. AUC estimates provide a measure of reinforcing efficacy in self-administration procedures using continuous schedules of reinforcement. Importantly, they may be used to quantify responding under conditions in which a dose-effect curve has both an ascending and descending limb [3]. For exercising rats, Pearson product-moment correlations were used to examine the relationship between heroin self-administration (as measured by AUC estimates) and wheel running (rev/day) before surgery (weeks 1–6), after surgery (weeks 7–9), during heroin testing (week 9), and throughout the duration of the study (weeks 1–9).

Results

No differences in body weight were observed between sedentary and exercising rats at any point during the study (data not shown). In exercising rats, wheel running increased over the first six weeks of the study until catheter implantation and the commencement of behavioral training (Fig. 1A). Wheel running stabilized during self-administration training with cocaine and then declined by approximately 50% during the final week of the study when heroin was tested. Sedentary and exercising rats did not differ in the number of cocaine infusions self-administered during the final day of training or in the number of saline infusions self-administered during the final week of the study (Fig. 1B). Heroin self-administration was characterized by an inverted U-shaped dose-effect curve in both groups [main effect of dose: $F(3, 99) = 10.976$; $p < 0.001$]. Exercising rats self-administered less heroin than sedentary rats [main effect of group: $F(1, 33) = 12.495$; $p = 0.001$], and this effect was most pronounced at lower doses of heroin [group × dose interaction: $F(3, 99) = 6.278$; $p = 0.001$]. Consistent with these observations, AUC estimates obtained from individual rats (Fig. 1C) revealed greater levels of responding in sedentary than exercising rats [$t(33) = 3.315$; $p = 0.002$]. Heroin self-administration (as measured by AUC estimates) was not correlated with wheel running before surgery (weeks 1–6), after surgery (weeks 7–9), during the week of heroin testing (week 9), or throughout the duration of the study (weeks 1–9).

Discussion

The principal finding of this study is that voluntary wheel running reduces the positive reinforcing effects

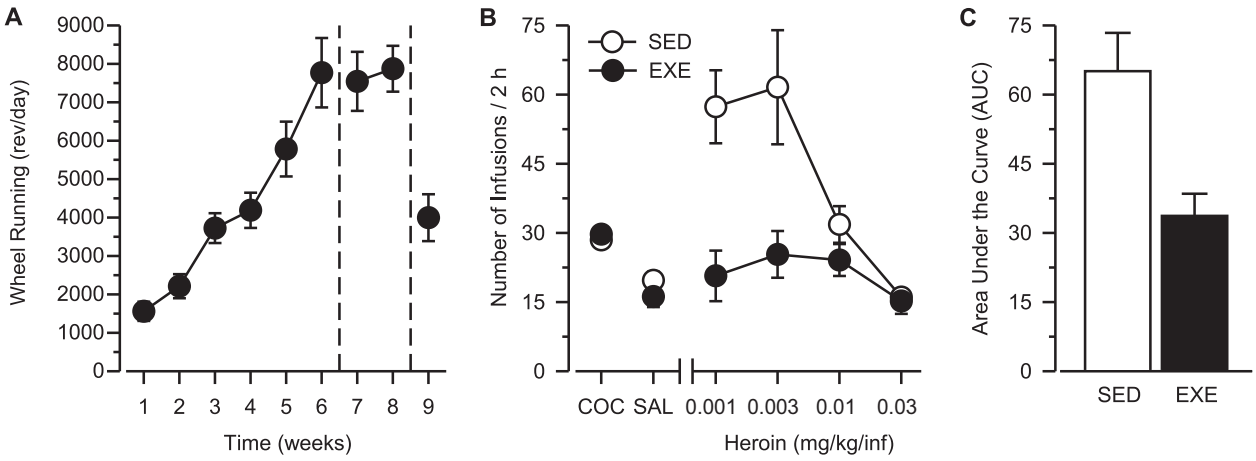

Fig. 1. (**A**) Wheel running over the course of the study in exercising rats (n = 18). Vertical axis depicts wheel running in revolutions per day (rev/day); horizontal axis depicts time expressed in "weeks" of 5- to 8-day intervals. Vertical reference lines after weeks 6 and 8 represent transitions between different experimental events: home cage and running wheel acclimation (weeks 1–6); self-administration training with cocaine (weeks 7–8); heroin self-administration (week 9). (**B**) Heroin self-administration in sedentary (open symbols; n = 17) and exercising (filled symbols; n = 18) rats. Vertical axis depicts number of infusions obtained during 2-h test sessions; horizontal axis depicts training dose of cocaine (COC; 0.75 mg/kg/inf), saline (SAL), and doses of heroin (0.001–0.3 mg/kg/inf). (**C**) Area under the curve (AUC) estimates derived from the heroin dose-effect curve for sedentary (SED; n = 17) and exercising (EXE; n = 18) rats. For all graphs, vertical lines surrounding data points represent the SEM; where not indicated, the SEM fell within the data point

of heroin in rats with an established history of drug self-administration. Wheel running increased during the first 6 weeks of the study, stabilized during behavioral training, and then declined by approximately 50% when heroin self-administration was initiated. Previous studies have reported that experimenter-delivered injections of opioid receptor agonists reduce spontaneous wheel running [15]; the present study extends those findings by showing that contingent (i.e., self-administered) injections of heroin also decrease physical activity. The reasons that running decreased when heroin was introduced are not known, but factors related to aerobic capacity, motor performance, and the reinforcing strength of wheel running may have played contributing roles [see 15]. We previously reported that wheel running prior to surgery and behavioral training was negatively correlated with cocaine self-administration on a progressive ratio schedule of reinforcement [17], and we expected that wheel running would be predictive of heroin self-administration in the present study. Contrary to our expectation, heroin self-administration was not correlated with wheel running during any phase of the study.

Hosseini et al. [9] reported that forced treadmill running for 90 min/day decreased responding maintained by 0.5 mg/infusion (~1.75 mg/kg/infusion) morphine, a moderate dose that falls on the descending limb of the dose-effect curve [see 19]. Decreases in responding maintained by a dose of a drug that falls on the descending limb of a dose-effect curve could indicate either a leftward shift in the dose-effect curve (i.e., an increase in potency) or a downward shift in the dose-effect curve (i.e., a decrease in efficacy). In the present study, exercise shifted the heroin dose-effect curve downward, decreasing responding at low and moderate doses to levels similar to those maintained by saline. AUC estimates, which quantify responding across the entire dose-effect curve, revealed that wheel running significantly decreased the reinforcing efficacy of heroin. Importantly, sedentary and exercising rats did not differ in cocaine self-administration on the last day of training or in responding during the saline substitution test. Thus, the effects of wheel running on heroin self-administration cannot be attributed to nonspecific effects on lever pressing or positively reinforced behavior.

Wheel running functions as a positive reinforcer [1], and the positive affective states produced by wheel running are reversed by the opioid antagonist naloxone [13]. Cosgrove et al. [4] reported that wheel running can serve as an alternative, nondrug reinforcer to decrease cocaine self-administration under concurrent access conditions. Although running wheels were never concurrently available during the self-administration sessions in the present study, the positive affective states produced by wheel running likely extended into the self-administration sessions. Concentrations of β-endorphin remain elevated up to 48 h following wheel running in well-trained subjects [8], and naloxone can precipitate opioid withdrawal symptoms after a night of wheel running in exercising animals [10, 18]. It is possible that endogenous opioid peptides released during nocturnal running substituted for the heroin stimulus during daily test sessions, thereby attenuating heroin self-administration much like methadone and other opioid receptor agonists attenuate heroin use in human populations.

The aim of this study was modest (i.e., to determine whether wheel running alters the reinforcing potency or efficacy of heroin), and future studies will be needed to identify potential mechanisms and determine the specificity of the observed effects. In the present study, all rats were trained with cocaine prior to testing with heroin. Cocaine and opioids produce complex interactions on both physical activity and drug self-administration [12], and future research should determine if running produces similar effects in rats trained with heroin. Physical activity also serves as one component of environmental enrichment, and enrichment is known to influence responding in drug self-administration procedures [7]. Future studies will need to determine whether other components of environmental enrichment (e.g., novel objects, social contact) produce effects similar to that of wheel running. In order to determine the specificity of these findings, the effects of wheel running will need to be examined on other measures of operant behavior, including general indices of gross behavioral output (e.g., locomotor activity), as well as responding maintained by nondrug reinforcers (e.g., saccharin). Finally, the effects of wheel running on heroin self-administration will need to be examined using other schedules of reinforcement (e.g., progressive ratio, second-order, concurrent choice), as different schedules of reinforcement measure different aspects of reinforcing strength.

From a translational perspective, these findings suggest that physical activity may be an effective intervention in the treatment and/or prevention of opioid abuse in clinical and at-risk populations. Al-

though the reasons that human populations self-administer heroin and other opioids are complex, any effective intervention will need to reduce the reinforcing efficacy of the drug relative to other stimuli in the individual's natural environment. The present data reveal that voluntary wheel running reduces heroin self-administration in rats with an established history of drug self-administration, indicating that physical activity reduces the positive reinforcing effects of heroin in some populations.

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