Pergamon

Pharmacology Biochemistry and Behavior, Vol. 51, No. 4, pp. 725-729, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00022-4

Exercise Attenuates Oral Intake of Amphetamine in Rats

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Received 5 August 1994

KANAREK, R. B., R. MARKS-KAUFMAN, K. E. D'ANCI AND J. PRZYPEK. *Exercise attenuates oral intake of amphetamine in rats.* PHARMACOL BIOCHEM BEHAV **51**(4) 725-729, 1995.—The effects of wheel running on oral intake of amphetamine were examined in six male Sprague–Dawley rats given a 0.075-mg/ml amphetamine sulfate solution as their sole source of liquid, six rats given a 0.15-mg/ml amphetamine solution, and four rats given water as their sole source of liquid. All animals were housed in Wahmann running wheels and adjoining cages, and had ad lib access to ground Purina Chow. For the first 7 days of the experiment, the doors to the running wheels were closed; the wheels were then opened for 6 days. This cycle was repeated a second time. Animals drinking the 0.15-mg/ml amphetamine solution consumed significantly less food and gained less weight than animals in the other two groups. Although there was no difference in food intake between rats drinking water and rats drinking the 0.075-mg/ml amphetamine solution, rats in the water group gained significantly more weight than rats in the 0.075-mg/ml amphetamine group. With respect to drug intake, rats consumed significantly less amphetamine when running in the wheels than when access to the wheels was prohibited. Access to running wheels did not alter water intake. These latter results suggest that drug intake can be reduced by the provision of an alternate behavior.

Amphetamine Exercise Running wheels Food intake Body weight gain

RESEARCH on the behavioral consequences of psychoactive drugs has examined both the pharmacological actions of the drugs and how environmental variables interact with these actions to influence behavior. Environmental variables such as the test situation, temperature, schedules of reinforcement, and nutritional conditions can modify the behavioral consequences of psychoactive drugs [e.g., (1,3,18,25,35)]. With respect to nutritional conditions, both food deprivation and access to palatable foods significantly affect drug self-administration (4–7,17,18). For example, Carroll and colleagues (5–7) reported that food deprivation dramatically increases self-administration of a number of psychoactive drugs including etonitazene, phencyclidine, amphetamine, and cocaine in both rats and monkeys. Removal of a palatable nutrient, such as sucrose, also can augment drug intake (4,5,17,18). As an example, rats consuming a standard laboratory diet and granulated sucrose dramatically increased their intake of either a morphine or an amphetamine solution when the sugar was removed (17,18). The effect of sucrose on drug intake was immediate and long lasting. Rats given alternate weeks of exposure to sucrose consistently decreased drug intake when the sugar was available, and increased intake when the sugar was removed.

One hypothesis that has been proposed to explain the effects of food deprivation and access to palatable foods on drug intake is that a general interaction exists between reinforcing substances. Removal of a reinforcing agent (e.g., sucrose) can elevate drug intake (18). One way to examine this hypothesis is to assess the effects of another behavioral event on drug intake. Previous research has demonstrated that rats will perform instrumental responses to obtain access to running wheels (8,32), indicating that activity can serve as a reinforcing event. Thus, in the present experiment, the effects of manipulating access to running wheels on oral intake of amphetamine solutions were investigated.

METHOD

Subjects

Sixteen male Sprague–Dawley rats (CD outbred, Charles River Laboratories, Wilmington, MA), weighing between 260 and 320 g at the start of the experiment, were used. Animals

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were housed individually in Wahmann (Timonium, MD) LC-34 activity wheels with adjoining cages. Wheel turns were monitored by a microswitch, positioned such that only complete 360° turns were recorded. Activity wheels were kept in a temperature (21 ± 1°C) and humidity-controlled room maintained on a 12L : 12D cycle (lights on 0700–1900 h).

Diet and Drugs

All animals were given ad lib access to ground Purina Chow in nonspill Wahmann LC-306 stainless steel food cups. Four rats received ad lib access to tap water, six rats to a 0.075-mg/ml *d*-amphetamine sulfate (Smith Kline and French, Philadelphia, PA) solution, and six rats to a 0.15-mg/ml amphetamine sulfate solution as their sole source of liquid. Water and the amphetamine solutions were presented in 100-ml graduated glass Richter tubes with nonspill stainless steel drinking spouts.

Procedure

To adapt animals to the laboratory environment, upon arrival all animals were housed in standard laboratory cages and given Purina Chow and water for 1 week. Animals were then placed in the running wheel cages with the doors to the wheels closed for 7 days. The doors to the wheels were then opened for 6 days. The doors wheels were again closed for 7 days, and then opened for an additional 6 days. Food and liquid intakes, body weights, and wheel turns were measured each day between 1700 and 1900 h.

Data Analysis

The running wheel broke for one animal in the water group on the first day that the wheels were opened for the second time. Therefore, the data from this animal were only included for the first 13 days of the experiment. Data for food and fluid intakes were analyzed using two-way analyses of variance (ANOVA) with type of drinking solution used as a between-groups measure, and wheel status, and the first and second time period of exposure to the wheels as within-subjects variables. Body weight gained across the experiment and feed efficiency were analyzed using one-way ANOVA. Wheel turn data were analyzed using a two-way ANOVA with type of drinking solution used as the between-groups measure, and the first and second period of running and days as within-subject variables. Data reported as significant have a value of $p < 0.05$.

RESULTS

Food Intake

Across the experiment, there was a trend ($p = 0.08$) for differences in mean daily food intake as a function of the drinking solution. Mean daily food intake of animals drinking water was 27.8 ± 2.7 g, of animals drinking the 0.075-mg/ml amphetamine solution, 27.4 ± 2.5 g, and of animals drinking the 0.15-mg/ml amphetamine solution, 20.6 ± 1.8 g.

Access to the running wheels significantly influenced food intake, $F(1, 13) = 24.43$, $p < 0.01$ (Table 1). Rats drinking either water or the 0.075-mg/ml amphetamine solution consumed significantly less food when allowed to run than when access to the running wheels was denied. A similar, but nonsignificant, trend was observed for rats drinking the 0.15-mg/ml amphetamine solution.

As indicated in Table 1, there were no differences in food intake as a function of whether it was the first or second time the wheels were opened or closed.

Body Weight

Body weight gained across the experiment differed significantly, $F(2, 12) = 15.73$, $p < 0.01$, as a function of the drinking solution. Rats in the water group gained 77.3 ± 7.1 g, rats drinking the 0.075-mg/ml amphetamine solution gained 29.5 ± 10.98 g, and rats drinking the 0.15-mg/ml amphetamine solution lost 37.3 ± 17.9 g.

An analysis of weight gained per 100 kcal consumed revealed a significant, $F(2, 13) = 12.26$, $p < 0.01$, difference among the groups. Although rats in the water group and those in the 0.075-mg/ml amphetamine group consumed similar amounts of food, a post hoc Tukey-Kramer HSD test demonstrated that rats in the water group gained significantly ($p < 0.05$) more weight per 100 kcal consumed (2.97 g/100 kcal) than rats in the 0.075-mg/ml amphetamine group (1.15 g/100 kcal). Rats drinking either water or the 0.075-mg/ml amphetamine solution gained significantly more weight per 100 kcal consumed ($ps < 0.01$) than rats drinking the 0.15-mg/ml amphetamine solution that lost 2.05 g/100 kcal consumed.

Examining body weight as a function of the availability of running wheels revealed that animals in all three groups gained weight when the wheels were closed and lost weight when the wheels were opened (Fig. 1).

Liquid Intake

Liquid intake varied significantly, $F(2, 13) = 22.85$, $p < 0.01$, as a function of the drinking solution. Averaged across the experiment, rats in the water group consumed significantly more liquid per day (44.8 ± 2.4 ml) than rats in either the 0.075-mg/ml amphetamine group (27.5 ± 3.3 ml) or the 0.15-mg/ml amphetamine group (22.2 ± 3.3 ml).

Access to the running wheels significantly affected liquid intake for animals in both drug groups. When the wheels were opened, rats drinking the 0.075-mg/ml solution consumed significantly, $F(1, 5) = 40.12$, $p < 0.01$, less liquid a day (19.7 ± 1.48 ml) and thus less amphetamine (1.48 mg) than when

TABLE 1

MEAN (±SEM) DAILY FOOD INTAKE AS A FUNCTION OF THE AVAILABILITY OF RUNNING WHEELS FOR RATS DRINKING WATER OR AMPHETAMINE SOLUTIONS

Drinking Solution	Wheels Closed-1	Wheels Opened-1	Wheels Closed-2	Wheels Opened-2
Water	33.6 ± 2.2 g	24.0 ± 0.3 g*	29.1 ± 1.7 g	24.4 ± 2.3 g*
Amphetamine (0.075 mg/ml)	32.0 ± 3.3 g	22.7 ± 3.9 g*	31.6 ± 2.3 g	23.1 ± 3.2 g*
Amphetamine (0.150 mg/ml)	21.1 ± 1.4 g	17.4 ± 3.8 g	24.3 ± 2.6 g	19.5 ± 2.6 g

*Food intake signficantly less ($p < 0.05$) when wheels opened than when wheels closed.

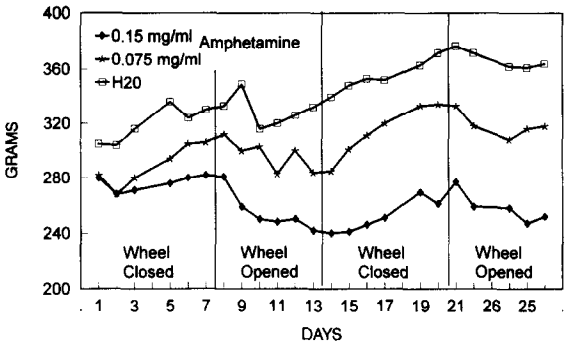

FIG. 1. Mean daily body weight for rats given either water, a 0.15-mg/ml, or a 0.075-mg/ml amphetamine solution as their sole source of liquid. Wheel closed indicates when access to running wheels was prohibited, and wheel opened when animals were allowed to run in wheels.

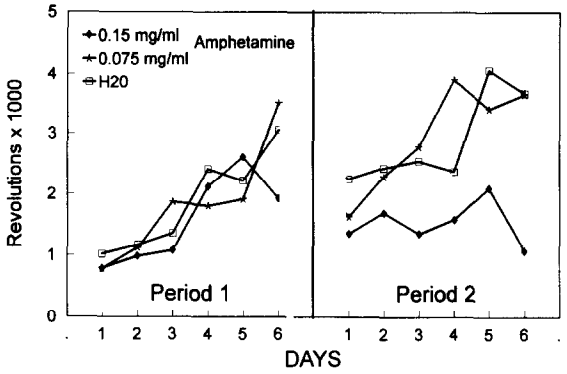

FIG. 3. Mean daily number of wheel turns made by rats given either water, a 0.15-mg/ml, or a 0.075-mg/ml amphetamine solution as their sole source of liquid. Period 1 indicates the first time, and period 2 the second time rats were allowed to run in wheels.

the wheels were closed (35.2 ± 3.2 ml; or 2.65 mg amphetamine) (Fig. 2). Similarly, when the wheels were opened, rats drinking the 0.15-mg/ml amphetamine solution drank significantly, $F(1, 5) = 16.20, p < 0.01$, less liquid per day (13.1 ± 4.1 ml) and thus less amphetamine (1.97 mg) than when the wheels were closed (31.3 ± 3.5 ml; or 4.70 mg/day amphetamine).

Although access to the running wheels did affect food intake of animals given water, the availability of exercise did not alter liquid intake of rats drinking water.

Wheel Revolutions

Mean daily number of wheel revolutions during each of the two periods with the wheels opened for each group of animals are shown in Fig. 3. During each period, the number of wheel revolutions increased significantly, $F(5, 10) = 5.55, p < 0.01$, as a function of days. Additionally, when collapsed across groups, rats ran significantly, $F(1, 12) = 6.06, p < 0.05$, more during their second exposure to the wheels than during their first exposure. Analysis of individual groups revealed that rats in both the water and 0.075-mg/ml amphetamine group ran significantly ($ps < 0.05$) more during the second exposure to the wheels than during the first. In comparison, no differences in wheel turns were observed as a function of exposure for rats drinking the 0.15-mg/ml amphetamine solution.

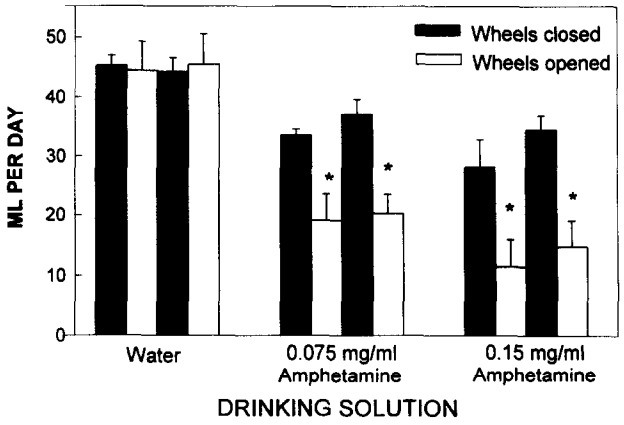

FIG. 2. Mean daily liquid intake as a function of availability of running wheels for rats given either water, a 0.15-mg/ml, or a 0.075-mg/ml amphetamine solution as their sole source of liquid. *Rats drank significantly ($ps < 0.05$) less liquid when the wheels were opened than when the wheels were closed.

DISCUSSION

The results of this experiment demonstrate that 1) oral intake of amphetamine reduces body weight gain and feeding efficiency, and 2) the availability of exercise alters oral amphetamine intake. With respect to the effects of amphetamine on body weight, across the experiment, animals drinking the amphetamine solutions gained significantly less weight on both an absolute basis and per kilocalorie consumed than rats drinking water. The effect on body weight gain was directly related to amount of amphetamine consumed, and thus was greater in rats drinking the 0.15-mg/ml amphetamine solution than in those drinking the 0.075-mg/ml solution. The effect on body weight was not simply due to the anorectic actions of the drug. Although rats consuming the 0.15-mg/ml amphetamine solution ate less food than rats drinking water, rats drinking the 0.075-mg/ml solution did not eat less than rats drinking water, but did gain significantly less weight. These findings are similar to those of previous studies demonstrating that rats given amphetamine are significantly less efficient at using calories for weight gain than controls [e.g., (15,16,24)]. These results indicated that amphetamine acts not only as an anorectic agent, but also alters metabolic processes. Amphetamine increases resting metabolic rate (16,33) and stimulates thermogenesis by increasing the binding of purine nucleotides in brown adipose tissue in rats (23). Thus, it can be proposed that the greater weight loss observed in rats drinking amphetamine is, at least partially, the result of the drug's ability to increase metabolic rate and/or thermogenesis.

As previously reported, the male rats drinking water in this experiment consumed less food and gained less weight when allowed to run than when access to the running wheels was prohibited (14,19,29,30). Similar alterations in food intake and weight gain as a function of the availability of the wheel were observed in rats drinking the amphetamine solutions. Thus, even though rats drinking the drug solutions took in approximately twice as much amphetamine when the wheels were opened than when they were closed, food intake and

weight gain were greater with the wheels opened. These results suggest that the anorectic effects of amphetamine are not simply the result of drug dose.

Access to running dramatically affected oral amphetamine intake. Rats drank significantly less of the amphetamine solutions when allowed to run in running wheels than when access to the wheels was denied. In contrast to amphetamine intake, water intake was not affected by the availability of the running wheels. The effect of providing access to the running wheels on amphetamine intake was very reminiscent of the effects of giving palatable foods to rats on amphetamine consumption (18). Rats consumed approximately 50% as much amphetamine when they were given access to either sucrose or running wheels than when these options were not available.

The effects of sucrose availability and exercise on drug intake are not limited to amphetamine. Previous studies have demonstrated that rats drink significantly less morphine when consuming sucrose (17) or given the opportunity to exercise [(28), Kanarek and Marks-Kaufman, unpublished results] than when these alternatives are not present. Additionally, it has been shown that availability of palatable foods and fluids can alter intake of other psychoactive drugs. For example, Lester and Greenberg (22) reported that rats previously accustomed to drinking alcohol stopped consuming alcohol when they were fed sucrose. When sucrose was removed, alcohol intake immediately increased. Sampson and colleagues (34) found that rats decreased responding for alcohol when sucrose was made concurrently available. Similarly, Carroll and colleagues observed that rats self-administered less etonitazene when a palatable glucose-saccharin solution was available than when it was not (5), and that rhesus monkeys self-administered less phencyclidine when given a saccharin solution to drink than when the solution was not available (4).

Recent research has demonstrated that intake of several classes of abused drugs also varies as a function of food availability (6,7,17). Rats and monkeys orally and intravenously self-administer smaller amounts of a number of psychoactive drugs (e.g., *d*-amphetamine, etonitazene, cocaine, and heroin) when given ad lib access to food than when food deprived. It has been proposed that restricted feeding regimes have similar effects in humans (12). In studies conducted during World War II on the effects of chronic semistarvation on physiological and psychological variables, young conscientious objectors substantially increased coffee and tea intake, cigarette smoking, and gum chewing as food deprivation progressed. Moreover, subjects who had never drank tea or coffee or smoked cigarettes became habitual users (20). It also has been hypothesized that chronic dieting can lead to binge eating when the dieter is exposed to "forbidden" foods (usually palatable foods containing large amounts of fat and/or sugar) (31). It is interesting to note that the prevalence of psychoactive substance abuse is greater in individuals with bulimia nervosa than in the general population (37). This finding again suggests an interaction between restriction of intake of palatable foods and psychoactive drug use.

The fact that the availability of palatable foods and exercise affects the intake of psychoactive drugs in both rats and monkeys, when the drugs are delivered either orally or intravenously, suggests that changes in drug distribution or metabolism cannot explain the decreases in drug intake observed when rats are given access to either sucrose or running wheels. Rather, the preceding findings support the hypothesis that a general interaction exists between reinforcing events. One obvious component of this interaction is that an animal cannot perform two competing behaviors at the same time (8). Thus, in the present study, animals could not drink while running in wheels. Although running restricted the time available to drink, the fact that no differences in liquid intake were observed as a function of wheel availability in rats drinking water indicates that time was not a primary factor in limiting liquid intake in rats drinking amphetamine.

It is possible that a common mechanism underlies the alterations in psychoactive drug consumption associated with exercise, access to palatable foods, and food restriction. Previous work has demonstrated that exercise (9,10), intake of palatable foods (11,26), and food deprivation (36) can enhance the activity of the endogenous opioid system. Additionally, acute intake of palatable fluids, short-term food deprivation, and exercise are associated with an apparently opioid-mediated decrease in pain sensitivity (2,13,21,27). Taken together, these results suggest that manipulations which increase opioid activity may lead to a reduction in intake of psychoactive drugs.

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