

Intake of Dietary Sucrose or Fat Reduces Amphetamine Drinking in Rats

ROBIN B. KANAREK,¹ WENDY FOULDS MATHES AND JEANNE PRZYPEK

*Department of Psychology, Tufts University, Research Building,
490 Boston Avenue, Medford, MA 02155*

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KANAREK, R. B., W. F. MATHES AND J. PRZYPEK. *Intake of dietary sucrose or fat reduces amphetamine drinking in rats.* PHARMACOL BIOCHEM BEHAV 54(4) 719-723, 1996.—The effects of intake of a palatable food source on oral amphetamine intake were assessed in adult male Long-Evans rats. In Experiment 1, six rats were given an amphetamine sulfate solution (0.1 mg/ml) and four rats were given water as their sole source of fluid. Rats were given a choice of chow and granulated sucrose for a week, alternated with weeks when only chow was fed. In Experiment 2, eight rats were given the amphetamine solution, and four rats water to drink. Rats were fed chow and hydrogenated vegetable fat for a week alternated with weeks when only chow was available. In both experiments, rats drank significantly less of the amphetamine solution when the palatable food choice was available than when given only chow to eat. Intake of palatable foods had a significantly smaller effect on water intake. In both experiments, rats drinking the amphetamine solution took in less fluid and less calories and gained less weight than rats drinking water. However, in Experiment 1, when sucrose was available, rats drinking amphetamine consumed a significantly greater proportion of their calories as sucrose than rats drinking water. Similarly, in Experiment 2, rats drinking the amphetamine solution chose a significantly greater percentage of their calories as fat than rats drinking water. These results demonstrate that intake of sucrose or fat leads to a significant reduction in amphetamine intake, and that the anorectic effects of amphetamine are not equivalent for different types of foods.

Amphetamine Sucrose Fat Drug self-administration Food intake Reinforcement Body weight
Nutrient selection

INTAKE of psychoactive drugs by experimental animals is influenced by a number of environmental variables including ambient temperature, reinforcement schedules, the test situation, housing conditions, and nutritional factors (1,10,16,20,26). With respect to nutritional factors, both food deprivation and the availability of palatable foods and fluids can significantly alter drug intake (2-4,15,16,19,24). In comparison to nondeprived animals, food-deprived animals self-administer significantly larger amounts of a number of psychoactive drugs, including amphetamine, etonitazene, phencyclidine, and morphine (4,5,15). Drug intake also increases when the availability of a palatable nutrient, such as sucrose, is limited (2,3,15,16). For example, Sprague-Dawley rats eating a standard laboratory diet (Purina chow) and granulated sucrose drank significantly more of either a morphine or amphetamine solution than when the sugar was not available (15,16). The effects of sucrose availability on drug intake occurred rapidly and were maintained over long periods of time.

All of the previous experiments examining the effects of palatable substances on drug intake used sweet-tasting foods

or fluids (2,3,15,16). Therefore, it cannot be determined if the alterations in drug intake observed as a function of food availability are specifically related to sweet tastes or represent a more general effect of palatable foods on drug self-administration. To determine if drug intake would be altered by other palatable foods, oral intake of an amphetamine solution was investigated as a function of the availability of a separate source of dietary fat. Rats prefer high-fat diets and gain excess body weight on these diets [e.g. (6,13)]. Additionally, more recent work has suggested that the orosensory properties of fats serve as positive reinforcing stimuli for rats and that these reinforcing effects may be mediated within dopamine containing systems in the central nervous system (CNS) (21,29,30).

Genetic factors may play a role in determining animals' responses to psychoactive drugs (5,22,26,28,32). For example, Carroll and colleagues (5) found that food deprivation enhanced drinking of the opioid drug, etonitazene by Wistar rats, but depressed intake of the drug solution by Sprague-Dawley rats. Previous experiments examining the effects of removal of palatable foods on drug intake have used Sprague-

¹To whom requests for reprints should be addressed.

Dawley rats (15,16). However, as strain differences can influence responses to psychoactive drugs, and additionally, it has been suggested that nonalbino rats may be more appropriate for drug tests than albinos (7), the present experiments examined the effects of nutrient availability on amphetamine intake in hooded Long-Evans rats.

GENERAL METHOD

Animals

Male virus and antibody free Long-Evans rats (CD outbred, Charles River Laboratories, Portage, MI) were used. Animals were housed individually in standard stainless steel hanging cages in a temperature-controlled room ($21 \pm 1^\circ\text{C}$), with a reverse 12 L:12 D cycle (lights on: 2000–0800 h).

Drugs

D-amphetamine sulfate (Smith Kline and French, Philadelphia, PA) was dissolved in water at a concentration of 0.1 mg/ml. The amphetamine solution was provided to the animals in 250 ml glass bottles with nonspill stainless steel drinking spouts.

Data Analysis

Data were analyzed using repeated measures analyses of variance. Post hoc comparisons between groups were made using the Bonferroni *t*-test. Data reported as significant have *p*-values of 0.05 or less.

EXPERIMENT 1

Procedure

Ten rats weighing between 275 and 325 g at the beginning of the experiment were used. All animals received ad lib access to ground Purina Rodent Chow No. 5001 (3.6 kcal/g). In addition, animals were randomly assigned to one of two drug conditions: four animals received ad lib access to tap water, and six animals received ad lib access to a 0.1% amphetamine solution as their sole source of fluid.

Each week for six weeks, half of the animals in each drug condition had ad lib access to granulated sucrose (4 kcal/g) in addition to chow. Every 7 days, the sucrose was removed from rats that had been consuming the sugar; and sucrose was

given to the animals that only had chow during the preceding week. Chow and sucrose were presented in Wahman (Timonium, MD) LC 306A food cups.

Body weights and chow, sugar, and fluid intakes were measured daily at the beginning of the dark portion of the 24-h cycle.

Results

Food Intake and Body Weight. Across the experiment, rats drinking the amphetamine solution consumed significantly less calories than rats drinking water, $F(1, 8) = 13.92, p < 0.01$. In both drug conditions, rats consumed more calories when consuming sucrose and chow than when eating chow alone, $F(1, 8) = 85.09, p < 0.01$ (Table 1). Caloric intake of rats given the amphetamine solution did not increase as a function of time indicating that tolerance to the anorectic effects of amphetamine did not occur in this study.

Examination of intake of chow and sucrose individually revealed that when both foods were available, rats drinking the amphetamine solution consumed a significantly greater percentage of their calories as sucrose and a smaller percentage as chow than rats drinking water, $F(1, 8) = 5.38, p < 0.05$. These differences were the consequence of rats given amphetamine consuming significantly less chow than rats drinking water, $F(1, 8) = 13.81, p < 0.01$. Absolute sucrose intake did not vary as a function of drug condition (Table 1).

Rats drinking amphetamine gained significantly less weight (89.8 g) across the experiment than rats drinking water (123.5 g), $F(1, 8) = 5.63, p < 0.05$.

Fluid and Drug Intake. Within diet and drug conditions, there were no differences in fluid intake as a function of week of the experiment. Therefore, water and amphetamine intakes, when rats were and were not consuming sucrose, were averaged across weeks for data analyses. Rats given the amphetamine solution drank significantly less fluid than rats drinking water, $F(1, 8) = 41.9, p < 0.01$ (Fig. 1). In both drug conditions, rats drank significantly less fluid when they were consuming sucrose than when the sugar was not available, $F(1, 8) = 105.95, p < 0.01$. Sucrose availability, however, had a more significant effect on amphetamine consumption than on water intake ($t = 3.41, p < 0.01$). Amphetamine intake was approximately 50% less when sucrose was available compared to when the sugar was not present. In comparison, water intake decreased by only 25% when rats were given sucrose to eat.

TABLE 1
MEAN (+ SEM) DAILY CALORIC INTAKE AND PERCENT SUCROSE INTAKE FOR RATS DRINKING AN AMPHETAMINE SOLUTION OR WATER

Drinking solution	Chow Intake (kcal)	Sucrose Intake (kcal)	Total Calories (kcal)	% Sucrose
Amphetamine				
Chow only	71.5 [†] ± 3.2		71.5* [†] ± 3.2	
Chow and sucrose	37.8 [†] ± 2.5	62.9 ± 4.3	100.7 [†] ± 6.1	62.4% [‡]
Water				
Chow only	87.7 ± 4.3		87.7* ± 4.3	
Chow and sucrose	62.1 ± 7.1	47.7 ± 9.8	109.8 ± 2.6	44.4%

* = Total caloric intake of rats within each drug condition significantly ($p < 0.05$) less when eating chow alone than when eating chow and sucrose.

[†] Chow intake and total caloric intake of rats drinking the amphetamine solution significantly ($p_s < 0.05$) less than that of rats drinking water.

[‡] % sucrose intake significantly ($p < 0.05$) greater for rats drinking the amphetamine solution than for rats drinking water.

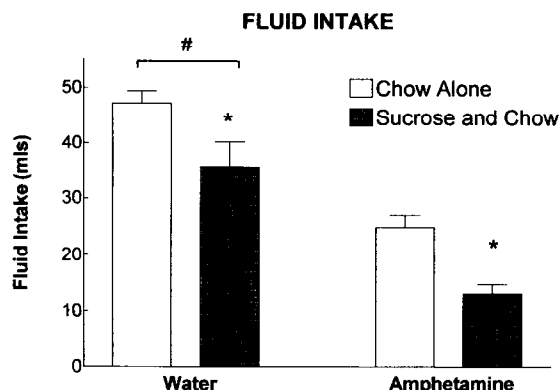


FIG. 1. Amphetamine and water intakes of rats when eating chow and granulated sucrose or chow alone. # = water intake significantly ($p < 0.01$) greater than amphetamine intake. * = water and amphetamine intake significantly ($p_s < 0.05$) less when rats consuming chow and sucrose than when eating only chow.

Rats drinking the amphetamine solution took in 1.31 mg/day of drug when eating chow and sucrose and 2.49 mg/day when eating only chow.

EXPERIMENT 2

Procedure

Twelve rats weighing between 200 and 225 g at the beginning of the experiment were used. All animals received ad lib access to Purina Rodent Chow No. 5001. In addition, animals were randomly assigned to one of two drug conditions: four animals received ad lib access to tap water, and eight animals received ad lib access to a 0.1% amphetamine solution as their sole source of fluid.

Each week for 4 weeks, half of the animals in each drug condition had ad lib access to hydrogenated vegetable fat (Crisco; 9.0 kcal/g) in addition to chow. Every 7 days, the fat was removed from rats that had been consuming it, and fat was given to the animals that only had chow during the preceding week. The fat was presented in 75 ml glass cups.

Body weights and chow, fat, and fluid intakes were measured daily at the beginning of the dark cycle.

Results

Food Intake and Body Weight. Rats drinking amphetamine consumed significantly less calories a day than rats drinking water, $F(1, 10) = 48.17$, $p < 0.01$. In both drug conditions, rats ate significantly more calories when eating chow and fat than when eating chow alone, $F(1, 10) = 97.25$, $p < 0.01$. Within dietary conditions, there were no difference in caloric intake as a function of week.

On a percentage basis when both fat and chow were available, rats drinking amphetamine consumed significantly more fat and less chow than rats drinking water, $F(1, 10) = 7.43$, $p < 0.05$. These differences were the result of rats in the amphetamine condition eating significantly less chow than rats in the water condition ($t = 5.97$, $p < 0.01$). No differences in absolute fat intake were observed as a function of drug condition (Table 2).

Across the experiment, rats given amphetamine gained significantly less weight (19.4 g) than rats drinking water (68.2 g).

Fluid and Drug Intake. Amphetamine intake was significantly lower than water intake throughout the experiment, $F(1, 10) = 67.52$, $p < 0.01$. When chow and fat were available, the rats in both drinking conditions drank significantly less fluid, $F(1, 10) = 81.03$, $p < 0.01$, than when only chow was available (Fig. 2). Amphetamine intake was significantly more affected by the fat availability than water intake ($t = 2.50$, $p < 0.05$). Amphetamine intake was decreased by 50%, while water intake was decreased by 28.9% when rats were eating chow and fat relative to when they were consuming only chow.

Rats drinking the amphetamine solution consumed 1.18 mg/day of drug when eating chow and Crisco, and 2.49 mg/day when eating only chow.

GENERAL DISCUSSION

The results of these experiments demonstrate that (a) the availability of palatable foods alters oral drug intake; and (b) the anorectic potency of amphetamine is not equivalent for different foods. With respect to the first conclusion, Long-Evans rats drank significantly less of an amphetamine solution when consuming chow and either sucrose or fat than when eating only chow. Although water intake was also lower when rats were eating chow and sucrose or fat than when they were eating chow alone, it was not decreased to as great a degree as amphetamine intake. One explanation for the decrease in water intake when animals were consuming sucrose or fat in addition to chow is that these dietary components may have led to an increase in the production of metabolic water. The oxidation of 1 g of protein produces 0.4 g of water, while the oxidation of 1 g of carbohydrate or fat produces 0.6 and 1.1 g of water, respectively (14). Because animals were consuming a larger portion of fat and carbohydrate when given a choice of fat or sucrose and chow, they would have obtained more metabolic water from the diet than when they were eating chow alone. However, the greater decrease in amphetamine intake than in water intake produced by these foods, indicate that the decrease in drug intake is not simply the result of an increase in the production of metabolic water.

The results of the present experiment are remarkably similar to those previously observed with Sprague-Dawley rats (16). When sucrose was available, intake of a 0.075 mg/ml amphetamine solution was reduced by 47%, and water intake by 25% in Sprague-Dawley rats (16). Previous experiments with Sprague-Dawley rats also suggest that the effect of sucrose on drug intake is dependent on the concentration of the amphetamine solution. When given a more concentrated amphetamine solution (0.15 mg/ml), Sprague-Dawley rats consumed 60% less amphetamine when eating sucrose than when not eating the sugar (Kanarek and Marks-Kaufman, unpublished results).

The present results illustrate that the effects of palatable foods on drug intake are not limited to sweet-tasting foods and fluids. Relative to when they were eating only chow, amphetamine intake was decreased to an almost identical degree whether animals were eating chow and fat or chow and sucrose. Additionally, recent work has shown that access to running wheels dramatically affects oral amphetamine intake (17). Rats took in approximately 50% less amphetamine when allowed to run in running wheels than when prohibited from running. In contrast to amphetamine intake, water intake was not affected by the availability of running wheels (17). Moreover, the effects of palatable foods on drug intake are not limited to amphetamine. Intake of sweet-tasting substances has been associated with reductions in oral intake

TABLE 2
MEAN (+ SEM) DAILY CALORIC INTAKE AND PERCENT FAT INTAKE FOR RATS
DRINKING AN AMPHETAMINE SOLUTION OR WATER

Drinking solution	Chow Intake (kcal)	Fat Intake (kcal)	Total Calories (kcal)	% Fat
Amphetamine				
Chow only	62.9 [†] ± 2.8		62.9 ^{*†} ± 2.8	
Chow and fat	32.5 [†] ± 3.1	79.2 ± 5.2	111.7 [†] ± 3.7	70.9% [‡] ± 3.6
Water				
Chow only	98.4 ± 4.7		98.4* ± 4.7	
Chow and fat	65.8 ± 5.9	68.2 ± 11.2	134.0 ± 5.1	50.9% ± 6.4

* Total caloric intake of rats within each drug condition significantly ($p < 0.05$) when eating chow alone than when eating chow and fat.

[†] Chow intake and total caloric intake of rats drinking the amphetamine solution significantly ($p < 0.05$) less than that of rats drinking water.

[‡] % fat intake significantly ($p < 0.05$) greater for rats drinking the amphetamine solution than for rats drinking water.

of a number of psychoactive drugs including morphine (15), phencyclidine (2) and alcohol (19,24).

Taken together, the previous results suggest that removing one rewarding experience (e.g., intake of palatable food or exercise) can lead to an increase in the intake of another reward (e.g., intake of psychoactive drugs). In support of this suggestion, other studies have shown that animals self-administered larger amounts of psychoactive drugs when they are food-deprived than when food is freely available (4,5,15). Restricting food intake may have comparable outcomes in humans. In research completed during the second World War on the effects of semistarvation on physiological and behavioral measures, conscientious objectors dramatically increased cigarette smoking, gum chewing, and intake of caffeinated beverages as deprivation progressed (18). Additionally, self-imposed food restriction (dieting) has been associated with binge eating when the individual confronts forbidden foods (i.e., palatable foods containing large amounts of sugar and/or fat) (23). Moreover, the prevalence of drug abuse is reported to be greater in individuals with bulimia nervosa than in the general population (31).

One possible explanation for the effects of palatable foods

on amphetamine intake comes from research examining the hypothesis that the neurotransmitter dopamine mediates the positive orosensory reinforcing effects produced by both sweet-tasting substances and dietary fats. More specifically, it has been proposed that ingestion of palatable foods increases the metabolism and release of dopamine in the central nervous system, and that synaptic activity at dopamine receptors is required to produce the hedonic effects of these foods (8,12,25,29,30). In support of this proposal, administration of dopamine receptor antagonists decreases intake of palatable sweet-tasting foods and dietary fat in a dose-related manner (8,25,29,30). Over the past 20 years a substantial body of evidence has accumulated indicating that the reinforcing properties of psychoactive drugs, such as amphetamine and cocaine, are the result of the ability of these agents to increase synaptic concentrations of dopamine in the central nervous system [e.g., (11,27,33)]. On the basis of this research it could be proposed that in the present experiments there was an additive effect of intake of palatable foods and amphetamine on central dopamine activity. Thus, less amphetamine would be required to produce its rewarding effects when animals were consuming sucrose or fat than when they were eating chow alone.

The present results also demonstrate that the anorectic potency of amphetamine is not equivalent for different foods. In both experiments, amphetamine intake was associated with a reduction in chow intake. However, relative to rats drinking water, rats drinking the amphetamine solution did not decrease either sucrose or fat intake. In fact, percent sucrose and percent fat intake were significantly greater in rats drinking the amphetamine solution than in rats drinking water. The selective increase in intake of sucrose and fat also may be mediated by amphetamine's actions on central dopamine. Previous work has shown that low doses of *d*-amphetamine selectively stimulate sugar intake while having no effect on chow intake (9). In comparison, *l*-amphetamine, which is less potent at releasing and blocking reuptake of dopamine than *d*-amphetamine but equipotent at releasing and blocking reuptake of norepinephrine, did not selectively affect sugar intake (9). This suggests that the effects of amphetamine on sucrose consumption are primarily the result of dopaminergic activity. The differential effect of amphetamine on chow intake and intake of sucrose and fat indicate that factors other than simple drug action must be considered when assessing the anorectic potential of amphetamine and similar agents. The nutrient

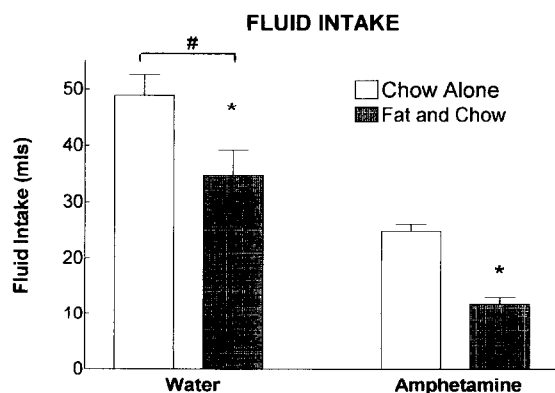


FIG. 2. Amphetamine and water intakes of rats when eating chow and hydrogenated vegetable fat or chow alone. # = water intake significantly ($p < 0.01$) greater than amphetamine intake. * = water and amphetamine intake significantly ($p < 0.05$) less when rats consuming chow and fat than when eating only chow.

composition and hedonic qualities of the foods may play an important role in determining the effects of anorectic drugs on ingestive behaviors.

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