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A High-Fat Diet Prevents and Reverses the Development of Activity-Based Anorexia in Rats

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Abstract

Objective—Activity-based anorexia is an animal model of anorexia nervosa in which limited access to standard lab chow combined with voluntary wheel running leads to hypophagia and severe weight loss. This study tested whether activity-based anorexia could be prevented or reversed with palatable foods.

Method—Male rats were divided into sedentary or ad libitum-running groups and maintained on 1 h daily access to standard chow plus one of the following: sugar, saccharin, vegetable fat (shortening), or sweet high-fat chow.

Results—Access to the sweet high-fat chow both reversed and prevented the weight loss typical of activity-based anorexia. Vegetable fat attenuated body weight loss, but to a lesser degree than the sweet high-fat diet. The addition of saccharin or sucrose solutions to the standard lab-chow diet had no effect.

Conclusion—The results suggest that certain palatable diets may affect the development of, and recovery from, activity-based anorexia.

Keywords

eating disorder; wheel running; sugar; fat

Introduction

Anorexia nervosa is a psychiatric disorder characterized by extreme hypophagia, body weight loss, and hypothermia.¹ Patients frequently show excessive exercising and compulsive activity.^{2,3} Anorexia nervosa is among the most life-threatening of all mental disorders, with a lifetime mortality rate between 5 and 20%, depending on the length of symptom duration.⁴ Effective treatments are greatly needed to combat this disorder.

The activity-based anorexia model, which was first described over 40 years ago,⁵ is used to study anorectic behavior in rodents and serves as an animal model of some features of anorexia nervosa. When given restricted access to standard rodent chow and *ad libitum* access to a running wheel, rats display high rates of wheel running and a voluntary reduction in daily caloric intake. Together, these behavioral changes induce significant weight loss,

hypothermia, loss of estrous cycle, stomach ulceration, and, without experimenter intervention, death from self-starvation and emaciation.^{6,7} In comparison, rats given *ad libitum* food and running-wheel access, and those with restricted food access but no running wheel, typically do not lose significant amounts of weight and can subsist normally.

Taste and palatability are key components in eliciting food intake.^{8,9} However, it appears that no reports have focused specifically on the effects of dietary manipulation in the prevention of activity-based anorexia. Palatable foods are known to be reinforcing and activate neurochemicals associated with reward, such as dopamine (DA) and the opioid peptides.^{10,11} These neurotransmitters have also been implicated in behaviors associated with activity-based anorexia and anorexia nervosa.^{12–15} It is possible, therefore, that palatable foods will have effects that potentiate the animals' motivation to eat. In this experiment, we test whether access to novel, palatable food (sugar, saccharin, high-fat, or a sweet high-fat chow) can reverse or prevent the development of activity-based anorexia.

Method

Subjects and Materials

Male Sprague–Dawley rats were bred at Princeton University from a stock originating from Taconic Farms (Germantown, NY) (Exp. 1) or obtained directly from Taconic Farms (Exps. 2–4). Prior to the onset of experiments, all rats were individually housed, provided with *ad libitum* access to standard laboratory rodent chow (LabDiet Rodent Diet no. 5001, PMI Nutrition, St. Louis, MO) (3.04 kcal/g, 12% fat, 60% carbohydrate, 28% protein) and water, and allowed to acclimate to a reversed 12-h light/12-h dark cycle for at least a week. Body weights were between 225 and 305 g (Exp. 1a), 320 and 350 g (Exp. 1b), 255 and 300 g (Exp. 2), 240 and 275 g (Exp. 3), and 285 and 355 g (Exp. 4) at the onset of the experiment.

Experimental Procedures

For each experiment there was a running group and a sedentary group. Animals in the running groups were individually housed in rodent cages connected to a running wheel (16 in. diameter) via a cylindrical passageway on one side of the cage (Lafayette Instrument, Lafayette, IN). The sedentary groups were housed in cages identical to those used by the running group, but without access to a running wheel. Prior to the onset of experiments, all rats were preexposed to daily 1-h standard chow access to adjust to the feeding schedule, during which time the running wheels remained closed for the running groups. After 3 days on the restricted-feeding schedule, the running wheels were opened, and dietary manipulations and data collection began as outlined in Table 1.

Each experiment was divided into three phases, with a change in diet as the independent variable. Measurements of chow intake and distance run during the hour of access were obtained during all phases, along with the distance run in 24 h. Body weight was measured prior to food access each day. During Phase 1, all rats were fed standard rodent chow pellets for 1 h/day (4th to 5th hour of the dark). When the body weight of the running groups fell to 75% of initial weight, Phase 2 began and the diet was switched to one of the following: Exp. 1: sweet high-fat chow (Research Diets no. 12451, New Brunswick, NJ; 4.7 kcal/g, 45% fat,

35% carbohydrate, 20% protein); Exp. 2: saccharin dissolved in tap water (0.1% concentration) along with standard chow; Exp. 3: 10% sucrose solution and chow (0.4 kcal/mL); and Exp. 4: vegetable fat (Crisco, J.M. Smucker Co., Orrville, OH; 9.2 kcal/g) and chow. After the same number of days passed, as prior to the initial diet switching, the rats were again provided with the initial standard chow diet (Phase 3). The experiment ended in Phase 3 if the body weight fell to 75% of the initial weight.

To control for the possibility that activity-based anorexia involves a conditioned taste aversion elicited by the initial pairing of a food with wheel running, Exp. 1b tested groups of rats given access to chow and the novel sweet high-fat diet in the reverse order.

Statistics

Measurements of standard chow, sweet high-fat chow, and vegetable fat in grams (g) and sucrose solution in milliliters (mL) were converted into kilocalories (kcal). For analyses of the distance run and kcal consumed, data were averaged for each rat within each dietary phase. Within-group comparisons were made using one-way repeated measures analysis of variance (ANOVA). Comparisons between the running and sedentary groups were analyzed using two-way repeated measures ANOVA. Newman–Keuls post-hoc tests were performed when justified.

Results

Exp. 1a: Access to a Sweet High-Fat Diet Restores Body Weight Lost Due to Activity-Based Anorexia While Increasing Both Running and Caloric Intake

In Exp. 1a, the running group's body weight steadily decreased when given access to the standard chow diet (Phase 1), and then increased when given access to the sweet high-fat diet (Phase 2), followed by losing weight again when given chow in Phase 3 ($F(25, 155) = 6.02, p < .0001$; Fig. 1A). A similar, but smaller, effect was observed with the sedentary group ($F(25, 155) = 131.4, p < .0001$; Fig. 1A). However, the running group's average body weight remained lower than that of the sedentary group throughout the experiment ($F(1, 10) = 33.86, p < .001$).

Caloric intake of the sweet high-fat diet provided in Phase 2 was significantly higher than that of the standard chow during Phases 1 and 3 for both the running group ($F(2, 17) = 149.9, p < .0001$, Fig. 2A) and the sedentary group ($F(2, 17) = 72.65, p < .0001$, Fig. 2A). Although a significant difference in calories was observed from one phase to the next within both the running and sedentary groups as a function of diet, there was no difference between the groups in terms of caloric intake.

There was a significant increase in mean distance run during the 1-h period of access to the sweet high-fat diet in Phase 2 ($F(2, 17) = 8.134, p < .01, 0.240 \pm 0.06$ km; Fig. 3) compared with Phase 1 (0.052 ± 0.02 km; $p < .01$) or Phase 3 (0.124 ± 0.02 km; $p < .05$) when given standard chow. In addition to the diet-dependent change in running during the hour of food access, 24-h running increased steadily across all three phases (Phase 1 = 3.62 km, Phase 2 = 6.06 km, Phase 3 = 8.43 km, $F(2, 17) = 11.89, p < .01$), mirroring the normal pattern of

excessive running activity when freely fed rats are given 24-h access to a running wheel.^{16,17}

Exp. 1b: The Effects of a Sweet High-Fat Diet are Not Due to Conditioning by the Initial Pairing of Running and Food

As seen in Figure 1B, the running group's body weight fell when the standard chow was available and rose when the diet was more palatable ($F(25, 155) = 6.018, p < .0001$). This occurred when the palatable diet was first given in Phase 1, or when it was first given in Phase 2 (as in Exp. 1a). The sedentary group showed a similar change in body weight ($F(25, 155) = 38.94, p < .0001$; Fig. 1B).

Both the running and sedentary groups consumed more calories when the sweet high-fat chow was available (Phases 1 and 3) compared with standard chow availability (Phase 2) (running group: $F(2, 17) = 147.3, p < .0001$, sedentary group: $F(2, 17) = 98.88, p < .0001$). Between-group comparisons revealed that the running group consumed less calories than the sedentary group when the sweet high-fat chow was available ($p < .001$), but not when the standard diet was available ($F(1, 10) = 17.86, p < .01$; Fig. 2B).

As in Exp. 1a, the running group ran about twice as far during the 1-h period of access to the sweet high-fat diet (Phases 1 and 3, 0.110 ± 0.02 km and 0.208 ± 0.09 km, respectively) relative to the days with access to standard chow (Phase 2, 0.071 ± 0.03 km), although these differences were not statistically significant. Also, like Exp. 1a, 24-h running increased steadily over time (Phase 1 = 0.875 km, Phase 2 = 2.70 km, Phase 3 = 4.71 km; $F(2, 17) = 10.25, p < .01$).

Exp. 2: Access to Saccharin Does Not Affect the Development of Activity-Based Anorexia

During Phases 1 and 2, rats in the running group lost weight compared with the sedentary group, in spite of saccharin being available in Phase 2 ($F(1, 14) = 30.62, p < .0001$; Fig. 4A). The original plan was to give the standard chow (no-saccharin) diet in Phase 3, but this was abandoned because rats in the running group reached their critically low body weights (75% of initial weight) without showing signs of increasing their food intake or recovering their body weight in response to saccharin access with their chow (Phase 2, days 11–15). The sedentary group successfully maintained a stable body weight through day 15.

There was no difference in saccharin intake between the two groups (running group: 5.02 ± 1.32 mL and sedentary group: 6.30 ± 1.81 mL). However, the running group ate significantly less chow than the sedentary group ($F(1, 14) = 27.2, p < .001$). This was evident during both Phase 1 when only the standard chow was available ($p < .0001$) and during Phase 2 when both saccharin and chow were available ($p < .001$).

Access to saccharin did not affect running during the 1-h feeding period (0.046 ± 0.013 km vs. 0.023 ± 0.009 km, Phase 1 vs. Phase 2, respectively). However, 24-h running increased significantly between the two phases (1.72 ± 0.29 km vs. 4.26 ± 1.17 km, respectively, $t(7) = 2.59, p < .05$).

Exp. 3: A Caloric Sweetener, Sucrose, Does Not Affect Activity-Based Anorexia

Results with 10% sucrose to drink were the same as with saccharin. During Phase 1, when standard chow was available, and Phase 2, when both sucrose solution and standard chow were available, rats in the running group lost weight compared with the sedentary group ($F(1, 12) = 16.4, p < .01$; Fig. 4B). Once again, the original plan to return to the standard chow (no-sucrose) diet (Phase 3) was abandoned because the running group all reached their critically low body weights during Phase 2 (days 7–13). The sedentary group successfully maintained a stable body weight throughout the 13 days.

There was no significant difference in sucrose intake between the running and sedentary groups (8.44 ± 1.85 mL and 9.73 ± 1.17 mL, respectively), but the running groups did eat more chow ($F(1, 12) = 54.21, p < .001$) during both Phase 1 ($p < .0001$) and Phase 2 ($p < .0001$).

Access to sucrose at mealtimes (Phase 2) did not have a significant effect on running during the daily 1 h of food access (0.018 ± 0.008 km vs. 0.057 ± 0.019 km, Phase 1 vs. Phase 2, respectively). Twenty-four-hour running increased over the two phases (0.87 ± 0.47 km vs. 3.18 ± 1.06 km, respectively; $t(5) = 3.62, p < .05$).

Exp. 4: A Non-Sweet, Vegetable Fat Attenuates the Effects of Activity-Based Anorexia

When vegetable fat and chow were available (days 8–21), both the running group and sedentary group gained weight during Phase 2. The running rats' weights reached a plateau during Phase 2 and decreased during Phase 3; the sedentary groups' body weights continued to increase into Phase 3 and eventually leveled off at a much higher weight than was ever reached by the running rats ($F(25, 250) = 19.78, p < .0001$; Fig. 4C).

There was no significant difference in vegetable fat intake between the running and sedentary groups (66.7 ± 5.26 kcal and 73.97 ± 18.47 kcal, respectively), but chow intake was greater for the sedentary group ($F(1, 10) = 29.91, p < .001$). This was evident when vegetable fat was available during Phase 2 ($p < .01$), and also when only chow was available during Phase 1 ($p < .001$) and Phase 3 ($p < .05$).

Access to vegetable fat in Phase 2 significantly increased running during the 1 h of daily food access ($F(2, 17) = 5.07, p < .05$), and as in the other experiments, there was a progressive increase in running in 24 h over the three phases ($F(2, 17) = 7.65, p < .01$).

Conclusion

The present results suggest that activity-based anorexia can be reversed or prevented by a sweet high-fat diet or the availability of pure vegetable fat. This orexigenic effect appears to be the result of a combination of sweet and fat, or fat alone, because access to sweet taste (saccharin or sucrose) was ineffective.

Several studies have investigated the role of conditioned taste aversion in the development of activity-based anorexia.^{18–21} The conditions necessary for conditioned taste aversion to occur are present in activity-based anorexia experiments.²² Rats are exposed to a

conditioned stimulus (CS), which is the taste of the novel food eaten during the feeding period, and then to the unconditioned stimulus (US) of wheel running. These pairings between the CS food and the wheel-running US are repeated a number of times during an activity-based anorexia procedure, and thus could result in conditioned taste aversion, which would tend to reduce food intake during the feeding period and thus might be a contributing factor in producing the activity-based anorexia effect. However, the results of the present experiments suggest that a conditioned taste aversion does not explain activity-based anorexia when the novel food is highly palatable. Caloric intake increased drastically when a novel sweet high-fat diet was made available during the hour of food access, even when the highly-palatable diet was paired with the running first, at the start of the experimental procedure (Exp. 1b).

The biological underpinnings of activity-based anorexia and anorexia nervosa are still unclear. Several neurotransmitter systems have been studied, notably, serotonin.^{23,24} However, DA and the opioids are also involved. Anorexic patients have decreased levels of the DA metabolite, homovanillic acid, as measured in cerebrospinal fluid,²⁵ and show alterations in DA receptors and their availability.^{26,27} Food restriction to 80% body weight in rats can lower extracellular DA in the nucleus accumbens to as little as 50% of normal.²⁸ Feeding normally releases extracellular DA in the nucleus accumbens in both normal and food-restricted rats.^{29–31}

Starved, underweight animals may overeat or “binge on” highly-palatable food partly to release DA when the mesoaccumbens DA system is depressed and extracellular DA is low in the NAc.³⁰ Bingeing on sweet or fat-rich palatable foods increases extracellular DA in the NAc,^{11,32} but intermittent access to standard rodent chow does not have this effect.¹¹ Low-body-weight rats that binge on sugar show enhanced DA release in the NAc compared with normal weight rats.³³ This “burst” of DA may further affect other DA-releasing behaviors such as wheel running,³⁴ which could account for the significant increase in running behavior during the hour of access to the sweet high-fat diet observed in Exp 1. Although intermittent access to sweet tastes have been shown to increase accumbens DA,^{11,35} sweet taste alone failed to affect activity-based anorexia in this experiment. Therefore, it appears that access to fat, or a combination of sweet and fat, produces neurochemical changes that can successfully reverse or prevent the genesis of activity-based anorexia.

The endogenous opioid peptides, β -endorphin, in particular, have also been implicated in activity-based anorexia and anorexia nervosa. Opioid peptides are increased by both exercise and food deprivation in rats.³⁶ The β -endorphin auto-addiction theory suggests that exercise-induced elevation in plasma β -endorphin in activity-based anorexic rats suppresses feeding, which further raises β -endorphin levels and elevates levels of running-wheel activity, leading to more severe food restriction and perpetuating a vicious cycle of weight loss.³⁶ Rats given an opioid receptor blocker demonstrate inhibition of wheel running in activity-based anorexia, implying a role for endogenous opioids in the maintenance of running.¹² In anorexic patients, alterations of β -endorphin in plasma and cerebrospinal fluid have been reported,^{37,38} and opioid antagonists have been successful in the treatment of some cases of anorexia nervosa.¹⁴ It is possible that changes in β -endorphin activity contribute to chronic food refusal in acutely ill anorexics.³⁷ Like food restriction, exercise

also stimulates the release of β -endorphin and other endogenous opioid peptides in humans.³⁹ The results of these studies support the activity-based anorexia model as an analogue for aspects of anorexia nervosa in humans, because in both rats and people, food restriction and excessive exercise appear to raise the levels of β -endorphin.

There are several possible explanations as to why a sweet-fat diet or a plain-fat diet may prevent and reverse activity-based anorexia. Activation of opioid systems has been linked to preferences for and consumption of sugars, fats, or sugar/fat mixtures, but not standard, less-palatable foods in both rats and humans.^{40–44} Therefore, it is possible that activation of some opioid system by palatable, fatty food may foster eating and weight gain. This is perhaps a different opioid system than the one that typically is activated by food restriction and running in activity-based anorexic rats. Although sugar intake alone can affect and is affected by opioids, it did not alter the development of activity-based anorexia in this experiment. It appears that the combination of sugar and fat, or fat alone, is necessary. The fat itself may be a critical factor by activating fat-sensitive feeding system, such as hypothalamic galanin, which is thought to reinforce behavior in part by releasing DA in the nucleus accumbens.⁴⁵

In conclusion, a diet rich in fat, with or without added sugar, can successfully reverse or prevent activity-based anorexia in rats, even though it makes them run more. The present results also indicate that a conditioned taste aversion does not develop in activity-based anorexia when the novel diet is highly palatable. These findings may contribute to further understanding the mechanisms underlying hyperactivity and self-starvation.

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FIGURE 1.

The body weight of rats from Exp. 1a (A) and 1b (B). (A) Rats with access to running wheels and chow for 1 h/day lose weight to ~75% of normal body weight (i.e. develop activity-based anorexia), but recover their weight when their diet is switched to a sweet high-fat chow in Phase 2. When the diet is switched back to standard rodent chow (Phase 3), running rats again lose weight and develop activity-based anorexia. Sedentary rats maintained on the same diet schedules gain weight rapidly with access to the sweet high-fat chow, and then plateau when the diet is switched to standard chow in Phase 3. (B) A similar effect on body weight is observed when the diet in Phases 1 and 3 is the sweet high-fat chow.

FIGURE 2.

Caloric intake in Exp. 1a (A) and 1b (B). (A) In Exp. 1a, when given access to the sweet high-fat diet (Phase 2), both running and sedentary rats increase their caloric intake during the 1 h of food access compared with the period when standard chow is available (Phases 1 and 3). (B) Similar results were observed in Exp. 1b when the sweet high-fat diet was presented during Phases 1 and 3, and standard chow was offered during Phase 2 (** $p < .001$).

FIGURE 3.

The distance run during the 1 h of food access for the rats in Exp. 1a. Rats increased the distance run during Phase 2 (about 1/4 km), during the hour when they had access to the sweet high-fat chow (** $p < .05$).

FIGURE 4.

Body weights for rats in Exps. 2–4. When running rats had access to standard chow plus (A) saccharin or (B) sucrose during Phase 2, they continued to lose weight, unlike the rats in Exp 1a (Fig. 1A). Sedentary animals maintained their body weight. When running rats had access to vegetable fat (C) with their standard chow they gained weight, although to a lesser extent than the rats given access to sweet high-fat chow (Fig. 1A). When switched back to standard chow in Phase 3, running rats again lost weight on standard chow, whereas sedentary rats maintained a stable body weight.

TABLE 1

Summary of dietary manipulations during the three phases of each experiment

Experiment	Groups	Phase 1	Phase 2	Phase 3
1a	Running ($n = 6$) Sedentary ($n = 6$)	Standard chow	Sweet high-fat chow	Standard chow
1b	Running ($n = 6$) Sedentary ($n = 6$)	Sweet high-fat chow	Standard chow	Sweet high-fat chow
2	Running ($n = 8$) Sedentary ($n = 8$)	Standard chow	Standard chow + saccharin solution	N/A
3	Running ($n = 6$) Sedentary ($n = 8$)	Standard chow	Standard chow + sucrose solution	N/A
4	Running ($n = 6$) Sedentary ($n = 6$)	Standard chow	Standard chow + vegetable fat	Standard chow