



## Simultaneous introduction of a novel high fat diet and wheel running induces anorexia

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### ABSTRACT

Voluntary wheel running (WR) is a form of physical activity in rodents that influences ingestive behavior. The present report describes an anorexic behavior triggered by the simultaneous introduction of a novel diet and WR. This study examined the sequential, compared with the simultaneous, introduction of a novel high-fat (HF) diet and voluntary WR in rats of three different ages and revealed a surprising finding; the simultaneous introduction of HF food and voluntary WR induced a behavior in which the animals chose not to eat although food was available at all times. This phenomenon was apparently not due to an aversion to the novel HF diet because introduction of the running wheels plus the HF diet, while continuing the availability of the normal chow diet did not prevent the anorexia. Moreover, the anorexia was prevented with prior exposure to the HF diet. In addition, the anorexia was not related to extent of WR but dependent on the act of WR. The introduction a HF diet and locked running wheels did not induce the anorexia. This voluntary anorexia was accompanied by substantial weight loss, and the anorexia was rapidly reversed by removal of the running wheels. Moreover, the HF/WR-induced anorexia is preserved across the age span despite the intrinsic decrease in WR activity and increased consumption of HF food with advancing age. The described phenomenon provides a new model to investigate anorexia behavior in rodents.

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### 1. Introduction

Activity-based anorexia is an animal model of anorexia, in which scheduled feeding, together with voluntary access to a running wheel, results in increased WR activity, hypophagia, and body weight loss [1]. As the feeding schedule becomes more restrictive, the WR activity increases, suggesting an inverse relationship between WR activity and food consumption [1]. Accumulating evidence suggests that both food consumption and voluntary WR share some neuro-behavioral characteristics of rewarding behavior. High-fat, sugar containing (HF) diets in particular have strong sensory appeals with reinforcing values, and hence are naturally rewarding [2]. When allowed to choose between HF diet and ordinary rat chow, rodents prefer HF diets and will consume a greater amount of calories when provided such diets [3,4]. Voluntary WR constitutes an activity behavior in rodents that affects ingestive behavior. The reinforcement value of food was reduced in rats with prior WR, while the reinforcing worth of running increased with food deprivation [5]. In our recent study, voluntary WR eliminated the dominant preference for HF food over chow diet, and the HF preference was restored when WR ceased.

Moreover, elimination of the HF dietary preference was not correlated with the degree of WR, indicating the obliteration of HF preference was more related to the behavioral aspect of wheel running rather than the physical activity aspect. Thus, WR activity appears to be both naturally rewarding and reinforcing [4–6].

Activity based anorexia requires the simultaneous presence of two conditions: restricted access to food and free access to running wheels [7]. Considering the strong influence of WR on rat behavior, we hypothesized that access to WR may be more critical than restricted access to food for the induction of anorectic-type behavior. For example, other manipulations of the diet, such as switching to a novel diet, rather than scheduled feeding, may also induce activity based anorexia. To this end, we examined if the simultaneous introduction of a novel HF diet along with running wheels alters food consumption in a different way than the separate or sequential introduction of the HF diet and WR. We further investigated differences between rats of three ages, ranging from young to aged.

### 2. Material and methods

#### 2.1. Experimental animals

Male F344×Brown Norway (F344×BN) rats aged 3 (young), 16 (adult), or 21 (aged) months old were obtained from Harlan

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Laboratories (Indianapolis, IN). Upon arrival, rats were examined and remained in quarantine for 1 week. Animals were cared for in accordance with the principles of the Guide to the Care and Use of Experimental Animals and protocols approved by the University of Florida IACUC committee. Rats were housed individually with a 12:12 h light:dark cycle (07:00 to 19:00 h). During the experimental period, rats were fed either a standard rodent chow (17% kcal from fat, 58% kcal from carbohydrate, 25% kcal from protein, 3.1 kcal/g, diet 7012, Harlan Teklad; Madison, WI) or an HF diet (60% kcal from fat, 20% kcal from carbohydrate (including 7% of the total kcal as sucrose), 20% of kcal from protein, 5.24 kcal/g, D12492, Research Diets, New Brunswick, NJ) or provided with both diets. All diets were provided *ad libitum*.

## 2.2. Experimental design

This study consisted of four experiments. The first experiment comprised adult rats ( $n=12$ ) accustomed to normal chow food and then provided running wheels for 3 days. At this point, the diet was switched from chow to HF, and half the rats allowed continued access to the running wheels and the other half denied access (sedentary).

The second experiment was similar to the first in that the adult animals ( $n=12$ ) were accustomed to normal chow, but then half the rats were simultaneously introduced to HF and provided running wheels, whereas the other half were introduced to HF and remained sedentary for 4 days. Separately, a third group ( $n=20$ ) was accustomed to the HF diet for 1 month and then half of the rats introduced to running wheels for 4 days and the other half remained sedentary.

In the third experiment, young and aged rats ( $n=6$ /group) were accustomed to normal chow and then simultaneously introduced to the HF diet (chow food removed) and provided access to running wheels for 3 days. At this point, the diet was switched back to chow while access to running wheels continued for 1 week. The experiment was repeated with only young rats ( $n=5-6$ /group); however, all rats were first introduced to the HF diet for 1 day, 2 days prior to the simultaneous introduction of the HF diet and running wheels or just the HF diet.

The fourth experiment was similar to the third in that a separate group of young and aged rats ( $n=6$ /group) were accustomed to normal chow and then simultaneously introduced to the HF diet and provided access to running wheels. However, in this experiment, chow food remained available throughout.

Body weight, food intake, and the extent of WR were recorded daily throughout the experiments. When the rats were provided access to both standard chow and the HF diet, consumption of both diets was determined separately by weight of food consumed. The position of the food trays containing the chow and HF food was alternated daily. Spillage of food was accounted for when calculating food consumption.

## 2.3. Wheel running

Rats were housed in cages equipped with Nalgene Activity Wheels (1.081 m circumference, Fisher Scientific, Pittsburgh, PA) and allowed free access to the wheel. Each wheel was equipped with a magnetic switch and counter. The number of revolutions was recorded daily and meters (m)/day calculated.

## 2.4. Statistical analysis

Data were analyzed by Student's *t*-test or one-way or two-way ANOVA. When the main effect was significant ( $p<0.05$ ), a Bonferroni post-hoc test was applied to determine individual differences between means. A *p*-value of less than 0.05 was considered significant.

## 3. Results

### 3.1. Experiment 1: Sequential introduction of WR and HF diet does not result in anorexia

Rats consumed a steady amount of chow, approximately  $54.1 \pm 2.2$  kcal/day ( $17.5 \pm 0.7$  g/day), prior to introduction of the running wheels (Fig. 1). During the WR phase on the chow diet, there was an expected decrease in food consumption of approximately 30% (Fig. 1). Wheel running during this period was  $202 \pm 21$  m/day, an expected amount for this rat strain and age [8]. When the HF diet (60% kcal from fat, 7% sucrose, 5.24 kcal/g) was introduced, there was an immediate hyperphagia in both rats with continued access to running wheels and those switched back to sedentary as measured by kcal consumption (Fig. 1) or gram consumption ( $22.5 \pm 0.9$  g/day, sedentary;  $20.4 \pm 2.3$  g/day, WR).

### 3.2. Experiment 2: Simultaneous introduction of WR and HF Diet results in anorexia

In Experiment 2, instead of sequential introduction of HF followed by WR, chow accustomed rats were simultaneously switched from chow to HF and allowed access to running wheels or switched to the HF diet and remained sedentary. With the latter, when the HF diet is introduced in the absence of WR, there is the expected hyperphagia (Fig. 2A, Sed/HF). Surprisingly, the rats simultaneously provided HF and running wheels immediately became anorexic, eating only a nominal amount of food (Fig. 2A, WR/HF). The HF-fed rats provided running wheels ran  $190 \pm 24$  m/day, an amount similar to the wheel running in Experiment 1 (Table 1). This experiment was terminated after 4 days to prevent excessive weight loss. When the running wheels were removed and the diet switched to chow, the rats immediately resumed eating at a level higher than the normal amount of chow diet (Fig. 2A, days 5 to 7,  $72.8 \pm 1.3$  kcal/day vs. days minus 3 to 0,  $51.0 \pm 1.8$  kcal/day,  $p<0.001$ ). This study was repeated in a separate set of virgin rats, in which the running wheels and HF diet were introduced simultaneously; however, in half the rats, the running wheel were locked to prevent WR. In this case, anorexia was observed in those rats that could run and not in the rats with access to only

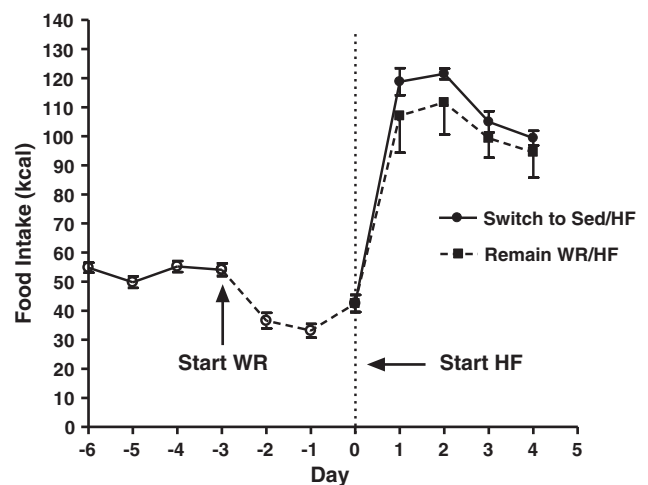


Fig. 1. Daily food consumption in kcal during three phases of Experiment 1: pre-experimental chow consumption (open circles), introduction of running wheels with continuation of the chow feeding (open circles, dashed line), and replacement of chow with the HF diet. At the initiation of the latter phase, the rats are divided into two groups, those in which the running wheels are removed (switch to Sed/HF, closed circles, solid line) and those with continued access to WR (remain WR/HF, closed squares, dashed line). Values represent the mean  $\pm$  SE of 6 rats per group. For remain WR/HF group, only lower standard error is shown.

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