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Vulnerability to diet-induced obesity is associated with greater food priming-induced reinstatement of palatable food seeking

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Abstract

We examined whether individual differences in weight gain during exposure to a “junk-food” diet were related to differences in later relapse-like behavior in a rat model. Following free access to a junk-food diet for 7 weeks, rats were trained to press a lever for palatable food pellets. Following extinction training, rats were tested for cue- and pellet priming-induced reinstatement. Results showed that rats prone to obesity while on the junk-food diet displayed greater pellet priming-, but not cue-, induced reinstatement relative to obesity-resistant rats, suggesting that obesity vulnerability is a factor determining one’s chances for some types of relapse.

Keywords

DIET-INDUCED OBESITY; FOOD SEEKING; REINSTATEMENT; RELAPSE

1. Introduction

Obesity is a pandemic and approaching tobacco use as the leading cause of preventable death in industrialized societies. A leading cause of obesity is the increased availability of highly processed, highly palatable foods [1, 2], which are typically high in calories, sugar, and saturated fat [3]. Although many individuals attempt to limit their intake of unhealthy foods through dieting, most relapse to their old, unhealthy eating habits relatively quickly [4, 5]. In fact, the World Obesity Federation recently referred to obesity as a “chronic relapsing progressive disease process.” [6]. Thus, as with the treatment of drug addiction, relapse prevention is a difficult challenge in the treatment of obesity. The development of improved treatment strategies requires a better understanding of the environmental, neural, and phenotypic determinants of relapse vulnerability.

To this end, we examined whether individual differences in weight gain during exposure to a “junk-food” diet were related to differences in later relapse-like behavior in rats. First, rats

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were separated into obesity phenotypes using a diet-induced obesity model that exposes outbred rats to a junk-food diet that results in excessive weight gain in a subgroup of rats [7, 8]. Next, rats were tested for relapse-like behavior using the reinstatement model of relapse [9, 10]. This classic model has been used extensively to study the environmental and neuropharmacological determinants of relapse and has face and predictive validity [11–16]. Because vulnerability to diet-induced obesity is associated with addiction-like neurobehavioral changes [17, 18], we hypothesized that obesity-prone (OP) rats would display greater relapse to palatable food seeking relative to their obesity-resistant (OR) counterparts.

2. Methods

2.1 Subjects and apparatus

Data were collected from experimentally naïve adult male, Sprague-Dawley rats ($n = 36$) weighing 280–310 g at the commencement of procedures and supplied by Envigo (Indianapolis, IN). Four rats were excluded from the study due to unreliable food-reinforced responding during training. Rats were housed under standard laboratory conditions (12-hr light cycle from 7:00 AM to 7:00 PM) with *ad libitum* access to standard chow (Lab Diet 5P07) and water in their home cages for the duration of the study. During the 7-week junk-food diet (see below) rats also had *ad libitum* access to a junk food mash. Rats were pair-housed upon arrival and until the end of the junk-food period, and then housed individually for the remainder of the study. All procedures were in compliance with NIH guidelines and were approved by the Bloomsburg University Institutional Animal Care and Use Committee.

All testing was conducted between 8:00 AM and 6:00 PM and occurred in standard modular operant conditioning chambers (Coulbourn Instruments, Whitehall, PA) that were housed in sound-attenuating, ventilated cubicles and connected to a PC with the Graphic State software interface system (Coulbourn Instruments). Each chamber is equipped with an active and an inactive response lever. Responses on the inactive lever are recorded, but have no programmed consequences. Chambers also include a house light, a row of multicolored LED cue lamps (above active lever), a tone generator, and a food tray (between the two response levers).

2.2 Junk-food diet and obesity classification

The study began by giving rats 7 weeks of *ad libitum* access to a mash made of Ruffles original potato chips (40 g), Chips Ahoy original chocolate chip cookies (130 g), Jif smooth peanut butter (130 g), Nesquik powdered chocolate flavoring (130 g), powdered Lab Diet 5P07 (200 g; % of calories: 18.56% protein, 15.79% fat, 65.65% carbohydrates), and water (180 ml). This diet was chosen based on previous studies [7, 18]. Rats did not have access to regular chow during this period. *K*-means clustering based on weight gain after 7 weeks on the junk-food diet was used as an unbiased method to identify OR and OP rats [19]. See Fig. 1 for schematic of experimental design.

2.3 Palatable food self-administration

Following the 7-week junk-food diet, rats were returned to a standard chow (Lab Diet 5P07) diet and trained to press the lever for food reinforcers contingent upon a fixed-ratio (FR)-1 schedule of reinforcement over the course of 1 to 2 days (this training period ended when 80 reinforcers were earned). Following initial training, rats responded on an FR-1 schedule during daily 2-hr sessions for 7 days. Each lever press resulted in delivery of a 45-mg food pellet containing 12.7% fat, 66.7% carbohydrate, and 20.6% protein (Catalogue # 1811155, TestDiet). This pellet type was chosen based on pellet preference tests conducted by Pickens et al. [20], in which it was determined to be the most preferred pellet. Delivery of the pellet was accompanied by a tone + flashing cue light conditioned stimulus (CS) presented for 5 s, which was followed by a 20-s time-out period signaled by illumination of the house light.

2.4 Extinction training and reinstatement testing

On the day following the last self-administration session, daily 2-hr extinction sessions began and continued for 10 days. During the extinction sessions, responses were recorded but had no programmed consequences (i.e., no CS or pellets). Following extinction, rats underwent 2-hr CS-induced reinstatement sessions. Conditions were identical to those of the self-administration sessions, except that lever presses did not lead to pellet delivery. To extinguish lever pressing before pellet priming-induced reinstatement sessions, rats underwent three daily sessions of extinction training (2 hr, with cue) that were identical to CS-induced reinstatement sessions. Next, animals underwent within-session pellet priming-induced reinstatement testing. The testing consisted of four consecutive 1-h sessions that were each identical to the CS-induced reinstatement sessions except that rats received two and four non-contingent pellets within the first minute of sessions 3 and 4, respectively. Session 2 served as the 0-pellet baseline. Data from session 1 were not used for the pellet priming analysis. This within-session procedure is based on previous studies with cocaine and pellet priming [21–24].

2.5 Statistical analyses

Data were analyzed using mixed factorial ANOVAs. The main dependent variable was lever pressing. Body weight while on the junk-food diet also was used as a dependent variable. Within-subjects factors included week of junk-food diet (0 through 7), session (CS-induced reinstatement session and preceding extinction session), number of pellets (0, 2, and 4; for pellet priming-induced reinstatement), extinction day (1 through 10), and lever (active and inactive). The between-subjects factor was obesity phenotype (OR or OP) as determined by *K*-means clustering. Because the factorial ANOVAs resulted in multiple main and interaction effects, we report only significant effects that are important for interpretation. All ANOVAs were followed by Bonferroni post-tests for multiple comparisons.

3. Results

3.1 Weight gain

Consistent with previous studies in rodents (e.g., [7, 25]), OR ($n = 26$) and OP ($n = 6$) rats did not differ in weight when given ad libitum access to standard chow (week 0; see Fig.

2A); however, after only one week of ad libitum access to the junk food diet, there was a significant difference in weight between groups, and this difference increased with each successive week [week X obesity phenotype interaction, $F(7, 210) = 38.43, p = .000$; main effect of obesity phenotype, $F(1, 30) = 33.13, p = .000$]. Because rats in the present study were pair-housed during the junk-food period, we could not measure food intake, but previous studies in rodents indicate that OP animals have greater caloric intake while on an obesogenic diet compared with OR rats (e.g., [17, 25–27]).

3.2 Self-administration and extinction

As shown in Fig. 2B, mean response rates and pellets earned were not significantly different across subsequent self-administration sessions for OR and OP groups. Mean response rates also were not significantly different across subsequent extinction sessions for OR and OP groups (see Fig.3A).

3.3 Reinstatement

As shown in Fig. 3B, active, but not inactive, lever responding increased significantly during CS-induced reinstatement tests compared to the last extinction session for both OR and OP groups [main effect of session, $F(1, 30) = 22.66, p = .000$; lever X session interaction, $F(1, 30) = 23.05, p = .000$], and there was no significant difference in the magnitude of reinstatement between groups. Active, but not inactive, lever responding also increased as a function of pellet priming for both OR and OP groups [main effect of priming, $F(2, 60) = 7.09, p = .002$; priming x lever interaction, $F(2, 60) = 8.24, p = .001$; see Fig. 4]. However, active, but not inactive, lever responding was higher for all pellet conditions for the OP group relative to the OR group [main effect of obesity phenotype, $F(1, 30) = 7.55, p = .010$; obesity phenotype x lever interaction, $F(1, 30) = 9.34, p = .005$]. The difference in responding between obesity phenotypes reached statistical significance only in the four-pellet condition according to the results of the Bonferroni post-tests. Thus, although active lever pressing was higher in all pellet conditions for obesity-prone relative to obesity-resistant rats (i.e., main effect of obesity phenotype), the greatest difference was observed in the four-pellet condition.

4. Discussion

The present results are the first to show that rats susceptible to diet-induced obesity show increased relapse-like behavior as assessed using the extinction/reinstatement model. To our knowledge, only two studies to date have assessed reinstatement of food seeking in animals with a history of obesogenic diet exposure, but neither study separated animals into obesity phenotypes. Chen et al. [23] reported that female rats with a history of cafeteria diet displayed *decreased* cue- and pellet priming-induced reinstatement compared with chow-fed rats. Similarly, Burokas et al. [28] found that male mice with a history of obesogenic diet exposure also showed decreased cue-induced reinstatement compared to chow-fed mice (pellet priming-induced reinstatement was not tested). Because a chow-only group was not included in the present study, it is not possible to determine whether rats exposed to a junk-food diet that are OP have increased vulnerability or, alternatively, whether OR rats have

reduced relapse vulnerability, a possibility that is suggested by the aforementioned studies. It will be important to test this possibility directly in future studies.

There appear to be overlapping neural mechanisms driving drug and food craving and relapse, especially with regard to the dopamine motive system [29–31]. Systemic and intra-nucleus accumbens injections of the dopamine D₁-like receptor antagonist SCH-23390 block cue-induced reinstatement of food seeking [32, 33], and intra-dorsal medial prefrontal cortex injections of the drug attenuate pellet priming-induced reinstatement of food seeking [34]. Using a method that allows identification of two distinct reward-associated ensembles within the same animal, it was recently shown that cue-induced seeking of either alcohol or saccharin activated ensembles consisting of largely overlapping neuronal populations within prefrontal cortex [35]. Moreover, relative to OR rats, OP rats show enhanced responsiveness of the mesolimbic dopamine system, as suggested by greater cocaine-induced locomotor activation [18, 26]. Behaviorally, OP rats display increased breakpoints on a progressive ratio schedule of palatable food reinforcement after the development of obesity [17, 27], as well as heightened conditioned approach to a sucrose cue before development of obesity [7]. The present results extend these findings by showing that OP rats also display increased pellet priming-induced food-seeking behavior during extinction, adding to the growing literature suggesting that excessive eating has much in common with drug addiction, including behavioral phenotypes and underlying physiological and neuroanatomical mechanisms [29, 36–38].

It is noteworthy that the increase in food seeking that we observed in OP rats was specific to pellet priming-induced reinstatement, in that no significant differences in self-administration, extinction responding, or cue-induced reinstatement were observed between OP and OR groups. These results support evidence that distinct neural mechanisms underlie food-reinforced operant responding (i.e., food self-administration) vs. reinstatement of food seeking [33, 39], extinction vs. reinstatement [40–42], and cue-vs. pellet priming- and drug priming-induced reinstatement [34, 43]. With regard to this latter distinction, although our results may appear incompatible with evidence that OP rats attribute more motivational value to food cues [7], it is noteworthy that food-associated discrete cues (CSs) were present during food priming in the present study. Thus, our results are compatible with the argument that priming by exposure to the primary reinforcer increases seeking by enhancing the incentive motivational properties of reward-associated cues [44, 45]. This hypothesis should be tested directly in future studies.

In summary, we used a diet-induced obesity model to show that OP rats display greater pellet priming-induced reinstatement of palatable food seeking compared with OR rats. From a translational perspective, our results suggest that those individuals with the greatest need for dietary treatment may also be those at greatest risk for diet recidivism. Future studies should investigate the environmental and neuropharmacological mechanisms underlying increased relapse vulnerability in OP individuals. Such investigations may lead to more targeted treatments for relapse to unhealthy eating habits in humans.

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Highlights

- The relationship between obesity vulnerability and relapse was investigated.
- Following junk-food diet exposure, relapse tests were conducted using a rat model.
- Food-primed reinstatement was greater in obesity-prone vs. obesity-resistant rats.
- Cue-induced reinstatement did not differ between obesity phenotypes.
- Thus, obesity vulnerability may predict some types of relapse vulnerability.

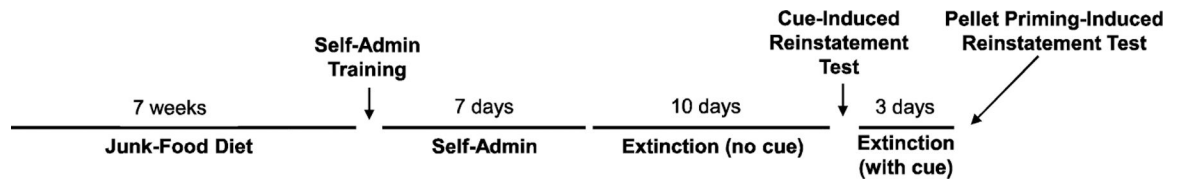


Fig. 1. Schematic representation of the experimental design for assessing the relationship between obesity phenotype and reinstatement of palatable food-seeking behavior.

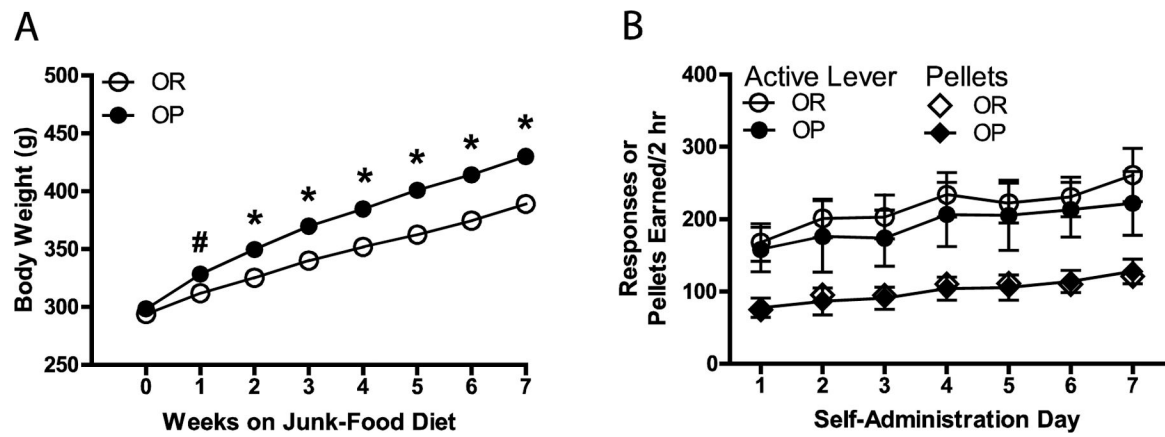


Fig. 2.

(a) Body weight across 7 weeks of a continuous junk-food diet in OR and OP rats. Rats were identified as OR or OP by means of *K*-means clustering based on weight gain after 7 weeks on the junk-food diet. (b) Responses and pellets earned across seven days of 2-hr palatable food self-administration sessions in OR and OP groups. Rats responded on an FR-1 schedule of reinforcement, and delivery of the pellet was accompanied by a tone + flashing cue light CS presented for 5 s, which was followed by a 20-s time-out period signaled by illumination of the house light. [#] $p < .05$ and ^{*} $p < .001$ compared to OR group, Bonferroni post-test. All data in figure are represented as mean \pm SEM. Points without error bars indicate the SEM is too small to illustrate.

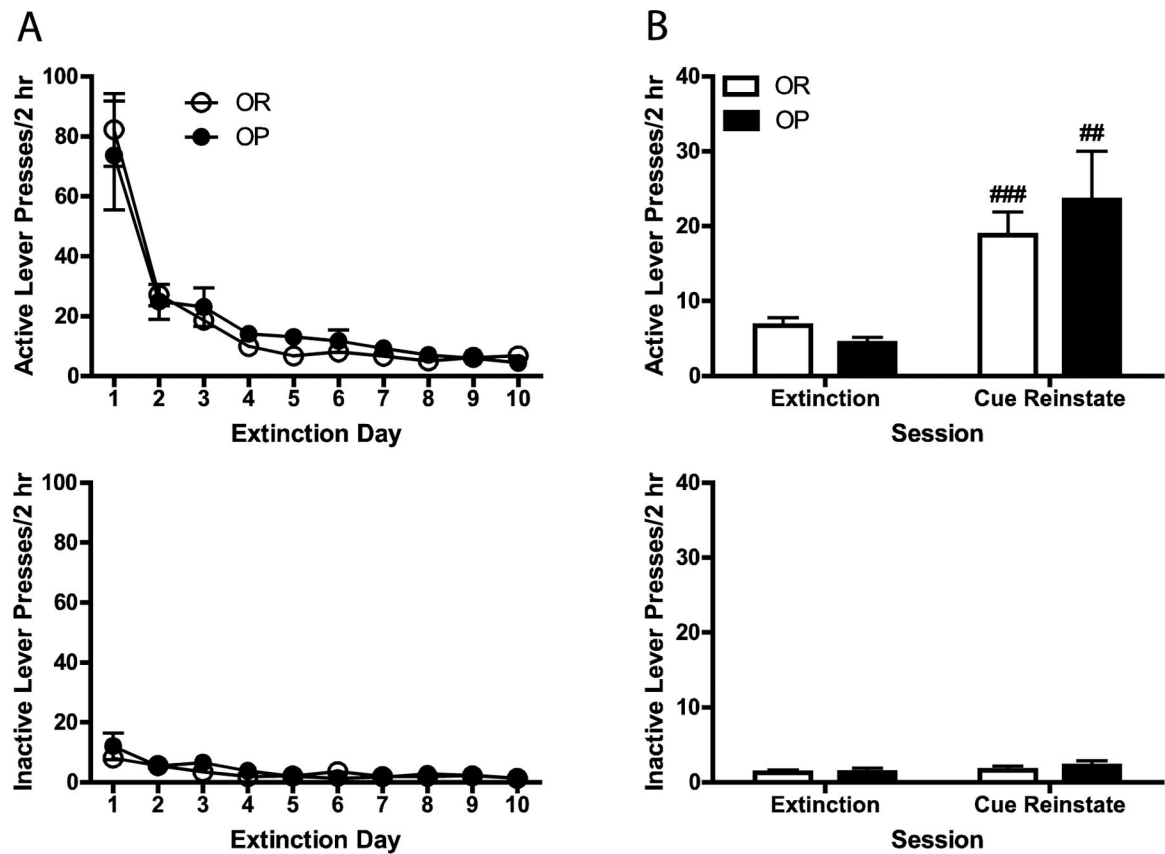


Fig. 3.

(a) Mean (\pm SEM) active and inactive lever presses across 10 days of 2-hr extinction training in OR and OP groups. Responses had no programmed consequences (i.e., no CS or pellets).

(b) Mean (\pm SEM) active and inactive lever presses during the last extinction session and CS-induced reinstatement testing in OR and OP rats. During reinstatement testing, conditions were identical to those of the self-administration sessions, except that lever presses did not lead to pellet delivery. ## $p < .01$ and ### $p < .001$ compared to extinction, Bonferroni post-test.

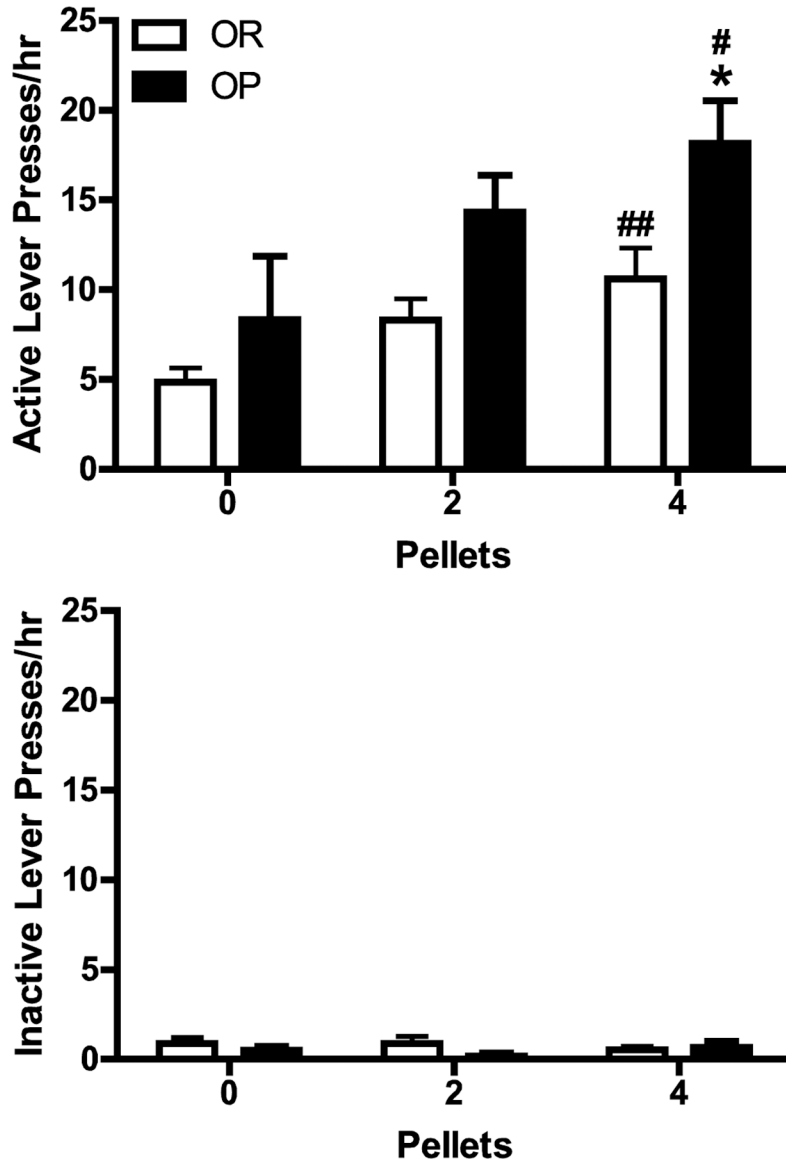


Fig. 4. Mean (+ SEM) active and inactive lever presses during pellet priming-induced reinstatement testing in OR and OP rats. The testing consisted of four consecutive 1-h sessions that were each identical to the CS-induced reinstatement sessions except that rats received two and four non-contingent pellets within the first minute of sessions 3 and 4, respectively. Session 2 served as the 0-pellet baseline. * $p < .05$ compared to OR group in 4-pellet condition; # $p < .05$ and ## $p < .01$ compared to 0-pellet condition, Bonferroni post-test.