Physiology & Behavior 213 (2020) 112729

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/physbeh

Toward isolating reward changes in diet-induced obesity: A demand analysis

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ARTICLE INFO

Keywords:
Behavioral economics
Demand behavior
Diet-induced obesity
Reward

ABSTRACT

Although hormonal and metabolic factors are well known to influence obesity, recent evidence suggests that obesity may be influenced also by changes in reward sensitivity akin to that seen in other 'reward pathologies', like substance use disorders. The current study sought to isolate changes in reward that may occur after the onset of diet-induced obesity by characterizing the economic demand for caloric (sucrose) and non-caloric (saccharin) reinforcers in a preclinical model of diet-induced obesity (DIO). We utilized economic demand analysis to measure baseline demand intensity (Q_0) and demand elasticity (α) for sucrose and saccharin reinforcers in rats. After baseline measures were collected, rats were assigned randomly to a high-fat (HF) diet or low-fat (LF) control diet. After 8-weeks of diet exposure, HF rats were divided into obesity-resistant (OR) or obesity-prone (OP) groups based on weight after the 8-week HF diet exposure. Post-DIO demand data for each reinforcer were reassessed. At baseline, rats had higher demand intensity and lower elasticity for sucrose compared to saccharin. After 8-weeks of the high-fat diet, OP rats had significantly greater weight gain and lower demand elasticity for sucrose and saccharin and higher demand intensity for saccharin. The changes in sucrose and saccharin elasticity suggest that DIO-induced changes in food-related behavior are associated with changes in reward processes. The changes in demand intensity for saccharin suggest that demand intensity, as a measure of 'set point', is not directly linked to metabolic processes. The current study shows that microeconomic theory and demand analysis is able to isolate independent aspects of diet-induced reward changes related to caloric and non-caloric reinforcers.

1. Introduction

Obesity is a growing world-wide problem with incidence in adults nearly tripling since 1975 [55] .To date, the majority of research on obesity has focused on the metabolic aspects (i.e., caloric intake and macronutrient distribution, hormonal signaling). However, recent evidence suggests that reward-related factors and associated brain changes also may play a role in obesity [52]. For example, obese individuals exhibit similarities in behavior relative to those with substance use disorders, although the focus is food rather than drug. Specifically, obese individuals show a lack of control over eating, difficulty achieving satiety, and an increased preoccupation with food [18,51]. Further, decreased dopamine D2 receptor signaling in the dorsal and ventral striatum as well as decreased baseline glucose metabolism in the prefrontal cortex are found in both those with substance use disorders and obese individuals [21,30,38,48,52,53]. Thus, reward-related brain dysfunctions may be related to the development and maintenance of obesity. However, the relative importance of reward-related vs. metabolic aspects of obesity currently is unknown. Specifically isolating the reward aspects of obesity from the metabolic aspects will further our understanding of the etiology.

Isolation of the reward aspects of obesity from the metabolic aspects (here specifically food nutrient content) may be accomplished by systematically comparing the value changes in a caloric reinforcer such as sucrose to those of a non-caloric reinforcer such as saccharin [45]. Saccharin is non-caloric and does not directly alter metabolism or energy balance [47]. Thus, a change in saccharin value, as a function of diet, amount of diet consumed, and weight gain, is related more directly to changes in reward sensitivity.

Consumer demand theory, a subset of microeconomics, has been used recently in clinical and preclinical research to better understand aspects of obesity including food consumption and value [19,42,43]. Demand analysis assesses the consumption of a commodity as a function of the price required to obtain it [28]. Generally, as the price of a commodity increases, the amount consumed decreases in a monotonic, positively-accelerated fashion [29]. At low price points, consumption is generally insensitive to price, i.e., inelastic; however, at high price points, consumption is generally sensitive to price, i.e., elastic [27].

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https://doi.org/10.1016/j.physbeh.2019.112729
Received 22 August 2019; Received in revised form 29 October 2019; Accepted 29 October 2019
Available online 31 October 2019
0031-9384/

Hursh and Silberberg [29] have formally characterized demand using the following exponential equation:

$$\log Q = \log Q_0 + k(e^{-\alpha Q_0 C} - 1) \quad (1)$$

where Q is consumption, Q_0 is consumption at zero cost, C is unit price, and α is demand elasticity. Using Eq. (1) to analyze consumption data has a major advantage in that it allows one to characterize not only how reinforcers are consumed when free (Q_0), but also how an organism will defend consumption of a commodity as a function of increasing price (α). Further, evidence suggests that reinforcer value is not a unitary construct inherent to goods themselves; rather, reinforcer value is multifaceted, where demand intensity (Q_0) and elasticity (α) measure different, independent reward processes [19,39]. Thus, by applying demand analysis to food consumption in models of obesity, it is possible to more accurately determine how conditions that contribute to obesity (both biological and environmental) specifically change these aspects of food reinforcement.

The aim of the current study was to isolate the reward-related aspects of obesity by measuring changes in sucrose and saccharin demand as a function of diet, diet consumption, and weight gain in diet-induced obese (DIO) rats. Further, we also determined if individual differences in pre-diet reward sensitivity, as measured by novelty seeking and demand elasticity (α) and intensity (Q_0) parameters, predicted future obesity.

2. Materials and methods

2.1. Experimental subjects

Male Sprague Dawley rats (N = 32; 250–275 g; age ~8–9 weeks) from Harlan Laboratories (Indianapolis, IN) were used in this study. All rats were individually housed in a temperature-controlled colony room with a 12–h light/dark cycle. All experiments were conducted during the light cycle. While in the home cage, rats were provided with standard chow (Teklad Global, Madison, WI; product #2918, protein = 18.6%; fat = 6.2%; carbohydrate = 44.2%; density = 3.1 kcal/g), high-fat (Research Diets Inc., New Brunswick, NJ; product #D12266B, protein = 16.8%; fat = 31.8%; carbohydrate = 51.4%; density = 4.41 kcal/g), or low-fat (Research Diets Inc., New Brunswick, NJ; product #D12489B, protein = 16.8%; fat = 10.6%; carbohydrate = 72.6%; density = 3.9 kcal/g) food and water *ad libitum*. All experiments were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

2.2. Apparatus

2.2.1. Operant chambers

Standard operant chambers (28 × 21 × 21 cm; ENV-008, Med Associates) with front and back aluminum sides, a Plexiglas sidewall, and a Plexiglas door were used. The chambers were placed inside sound-attenuating cabinets (ENV-018 M, Med Associates). Each operant chamber contained one recessed food receptacle with a liquid dispenser and a magazine light (5.1 × 5.1 cm; ENV-202RMA) located 2 cm above the chamber floor on the front aluminum wall. On each side of the food receptacle, there were two retractable response levers (4.5 cm; ENV-112CM) 6 cm above the floor with a white cue light (ENV-321 M) 6 cm above each lever. Located above the top left cue light was a Sonalert tone generator (ENV-223 AM) and located above the top right cue light was another Sonalert tone generator (ENV-223 HAM). A white house light (ENV-315 M) was located on the back wall of the chamber 17 cm above the floor. Two nosepoke response receptacles (ENV-114 M) were located on both sides of the back wall across from the front response levers. A syringe pump (PHM-100) located outside of the sound-attenuated chamber was used to deliver varying volumes (mL) of sucrose (Sigma Aldrich, St. Louis, MO; product #S9378) or saccharin (Sigma Aldrich, St. Louis, MO.; product #S1002). A computer equipped with Med-PC controlled all scheduled consequences and recorded all responses. All manipulanda in the operant chamber were mentioned here only to describe the specific environmental context where the experiments were conducted. However, only the two levers, the liquid dispenser, and the magazine light were used in this study.

2.2.2. Locomotor chambers

Locomotor activity was recorded using an animal activity monitoring system with Digipro System software (AccuScan Instruments, Columbus, OH). The chambers were 42 × 42 cm square and were surrounded by 30 cm high acrylic walls. Each chamber was equipped with 16 × 16 cm grid photo beam sensors 2.5 cm apart and 7 cm above the chamber floor. Horizontal activity was recorded for a 30-min period comprised of six 5-minute blocks. Activity was measured as photo beam interruptions and was expressed as total distance traveled (cm).

2.2.3. Conditioned place preference (CPP) chamber

A 3-compartment CPP chamber (28 × 21 × 21cm; Med Associates) located in a sound-attenuating cabinet (ENV-018 M; Med Associates) was used. Guillotine doors separated the 3-compartments of the chamber. The middle compartment had gray walls and smooth gray PVC floor (12 × 21 × 21 cm). The two end compartments (28 × 21 × 21 cm) had different contexts: one compartment had black walls and a stainless steal grid floor, and the other had white walls with a stainless steal mesh floor. A computer with Med-PC software controlled the experimental session.

2.3. Diet-induced obesity model

In order to study the behavioral and biological mechanisms that contribute to obesity, we used the DIO model. This model has been well established and is highly translational in that it allows for differential weight gain of individuals consuming the same diet, an aspect often seen in human obesity [10,31–33]. The DIO model separates rats fed a high-fat (HF) diet into two groups: obesity prone (OP; top 1/3 in weight) and obesity resistant (OR; bottom 1/3 in weight) based on weight at the end of an 8-week period [12]. Rats were weighed every day, as was the amount of food eaten (100 g of food was available in every home cage, which was more than a given rat ate in a 24 h period). Low-fat (LF) diet group of rats served as control; their food also was weighed every day.

2.4. Initial training and pre-diet demand behavior

All animals (N = 32) were first magazine shaped (i.e., trained as to where sucrose and saccharin would be delivered) and lever trained (with active and inactive lever present) using 0.2% saccharin or 10% sucrose (counterbalanced; [56]). After rats showed a discrimination ratio of at least 80% for the active lever with both reinforcers during lever training they were moved on to the demand procedure before being fed the low-fat and high-fat diet. In this procedure, two levers were presented in the operant chamber however only one lever was active (counterbalanced; active lever stayed the same as in lever training for a given rat). Responses on the inactive lever were recorded but produced no consequence. By pressing one of the levers (FR1,counterbalanced), the rats earned 0.2% saccharin or 10% sucrose (counterbalanced) paired with a magazine light. Each session lasted 10 min and rats consumed an unlimited amount of the respective reinforcer within that time. Unit price (defined as the response requirement divided by the volume available, standardized and expressed as per max unit) was increased as a function of session by decreasing the volume of saccharin or sucrose from 0.1 mL to 0.0017 mL in quarter-log steps, while keeping the ratio requirement constant at FR1 for a terminal unit price sweep from 1–50 [25,56]. Reinforcer consumption obtained across sessions was determined for all rats in order to measure the baseline demand intensity (Q_0) and elasticity (α) of sucrose and

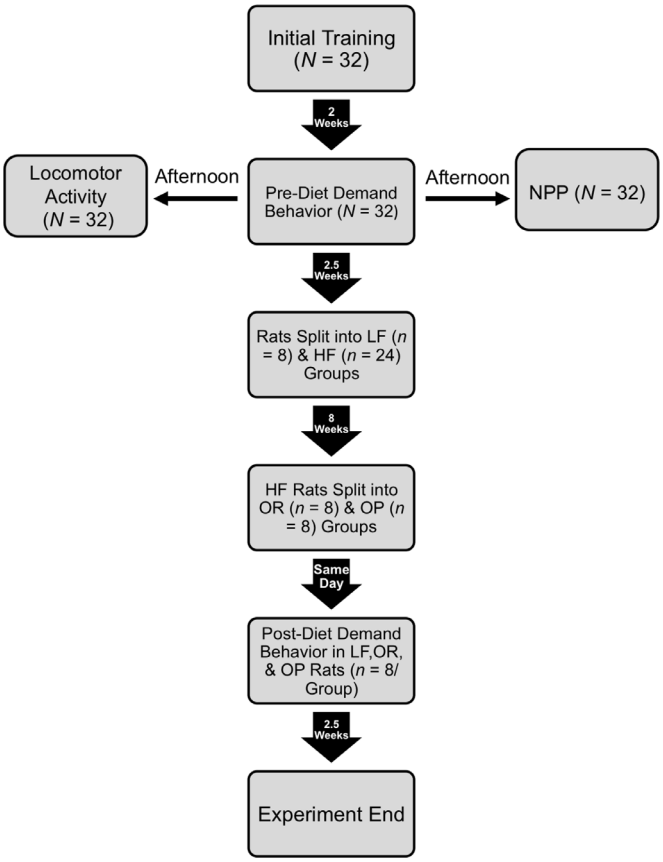

Fig. 1. Timeline of Experimental Events. Rats (N = 32) first went through initial training. After two weeks, baseline demand behavior was collected in the morning while locomotor behavior and NPP behavior were collected in the afternoon. Rats were then given a LF (n = 8) or HF (n = 24) diet for 8 weeks. After the 8-week period, rats were placed in to OR (n = 8) and OP (n = 8) groups based on weight. Post-diet demand behavior was then collected on OP, OR, and LF rats for ~2.5 weeks.

saccharin. During the period of assessing baseline demand, all rats received a standard chow diet. See Fig. 1 for a timeline of all experimental procedures.

2.5. Measuring novelty seeking: novelty-induced locomotor activity

Greater novelty seeking is a feature shared by obese individuals and those with substance use disorders [50] and is predictive of drug reward sensitivity in animal models [40]. To determine if novelty seeking at baseline prior to the diet was predictive of weight gain, amount of diet consumed, and/or demand parameters after the 8-week diet, we used locomotor activity to assess inescapable novelty [9]. After the baseline demand assessment, locomotor data were collected one time. Rats were placed into locomotor chambers and locomotor activity was measured for 30 min. Generally speaking, these data are interpreted as the greater the total distance traveled, the greater novelty seeking for a given rat [35].

2.6. Measuring novelty preference: novelty place preference (NPP)

We used NPP to assess novelty preference, another aspect of novelty seeking independent of novelty-induced locomotor behavior [5,15]. NPP data were collected after baseline demand and locomotor activity data. Specifically, rats were habituated to a given compartment (counter balanced) in the 3-compartment NPP apparatus for two days. On the third day, rats were placed in the middle gray compartment and the doors to both sides of the chamber were opened. NPP was defined as the amount of time spent in the novel compartment of the NPP chamber, with greater novelty preference measured as greater time spent in the novel compartment.

2.7. Demand behavior after 8-weeks of high-fat or low-fat diet

Following initial training and baseline behavior, rats were fed their respective diets over an 8-week period. Eight control rats were given a LF diet and 24 rats were given a HF diet. Rats were matched for pre-diet demand performance, i.e., there were no statistical differences in average demand behavior for either pre-diet sucrose or saccharin between groups that were subsequently given the HF or LF diets. After the 8-week exposure to the diets, rats fed the high-fat diet were further divided into OP (n = 8) and OR (n = 8) groups based on body weight. Rats falling in the middle 1/3 of body weight were repurposed to another study. After rats were divided into their respective groups, demand data were collected again with 0.2% saccharin and 10% sucrose (counterbalanced), as determined for baseline behavior. This design allowed for analysis of the change in demand intensity (Q_0) and elasticity (α) as a function of weight gain from baseline. Note that rats were kept on their respective LF and HF diets after the 8-week period while post-diet demand data were collected.

2.8. Data analysis

Consumption was defined as the number of responses per session x the volume (mL) of the reinforcer earned during that session. Consumption data were analyzed as a function of increasing unit price using R statistical software version 3.4.2 (R Foundation for Statistical Computing) for Mac OS X by fitting Eq. (1) to the data via nonlinear mixed effects modeling (NLME; [4,41,57]), with Q_0 and α as free parameters and k (scaling factor) as a global constant (best-fit k across all conditions). The NLME models defined reinforcer solution (i.e. sucrose or saccharin) as a fixed, nominal within-subjects factor, diet as a fixed, nominal between-subjects factor, and subject as a random factor.

NLME is a hierarchical, multilevel modeling technique that uses maximum likelihood estimation [37] to determine parameter estimates of predefined non-linear functions over different experimental conditions (fitting models to each individual). NLME provides metrics of goodness-of-fit and determines statistical significance of parameter estimates across levels of experimental conditions. Note that NLME is superior to traditional ANOVA in that it significantly increases power, decreases type I error rates, and aids in interpretation due to the use of defined functions that can describe underlying relationships in the data [4,57]. Models were compared using Akaike information criterion (AIC) values. Using ΔAIC values (the difference in AIC values between models), evidence ratios for the best model were compared to the second-best model [13,14]. The evidence ratios indicated the relative goodness-of-fit of the best model to the second-best model, and only statistics from models with the highest evidence ratios were reported. Statistical significance was defined as $p < 0.05$ and all interactions were probed using contrasts. For weight data, Student's t-tests and ANOVAs were used; Tukey HSD post-hoc tests were used to probe interactions with significance defined as $p < 0.05$.

3. Results

3.1. Pre-diet demand behavior for sucrose and saccharin

The pre-diet output and demand curves are shown in Fig. 2A and 2B, respectively. NLME analysis (best-fit global k = 2.54) revealed a significant main effect of reinforcer, with greater Q_0 estimates for sucrose [$F(1, 473) = 3.91$, $p = 0.049$]. A main effect of reinforcer for α was found, with smaller α estimates for sucrose [$F(1, 473) = 9.65$, $p = 0.002$]. In summary, these results suggest that sucrose had a greater demand intensity (Q_0) and lower elasticity (α) compared to saccharin

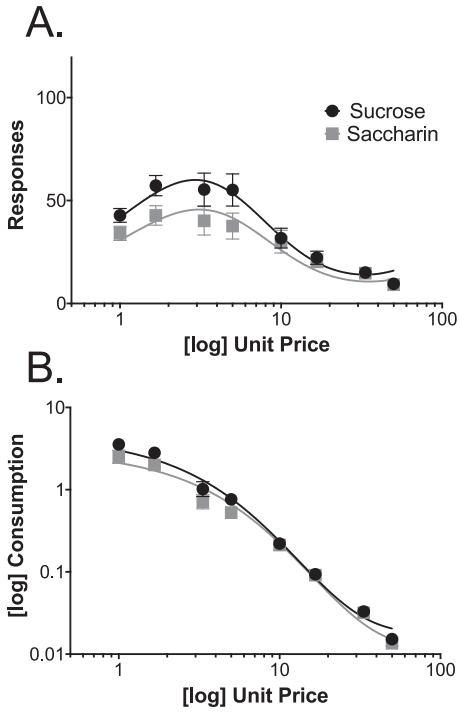

Fig. 2. Pre-Diet Output and Demand Curves. (A) The maximum output (number of responses) for sucrose (black circles; Omax = 62.64) is greater than the maximum output for saccharin (grey squares; Omax = 47.35). Data presented as mean ± SEM. **(B)** The demand intensity (Q_0) is greater and the demand elasticity smaller (α) for sucrose (Q_0 = 5.90; α = 0.017) compared to saccharin (Q_0 = 4.68; α = 0.019), $^*p < 0.05$. Data presented as Log mean ± SEM. In both figures, data points represent average behavior. For output curves, smooth lines represent drawn output functions via NLME-determined demand model parameters of best fit. For the demand curves, the smooth lines represent NLME-determined models of best fit. For each reinforcer N = 32.

prior to diet exposure.

3.2. Pre-diet behavior correlations

The maximum output (Omax) for sucrose and saccharin were calculated (see [56]) from pre-diet demand parameters (see Fig. 2A for the output curves) and were correlated with each other. Fig. 3A shows that the Omax for sucrose and saccharin were correlated positively (r = 0.83, $p < 0.0001$), suggesting that rats with greater maximum responses for saccharin also had greater maximum responses for sucrose. Additionally, Fig. 3B shows that the α for sucrose and saccharin (see Fig. 2B for demand curves) were correlated positively (r = 0.88, $p < 0.0001$), suggesting that rats that exhibited less elastic sucrose demand also exhibited less elastic saccharin demand. Pre-diet Omax values for sucrose and saccharin were correlated with pre-diet locomotor behavior. Fig. 3C and 3D show that locomotor behavior was correlated positively with both sucrose Omax values (r = 0.31, p = 0.04) and saccharin Omax values (r = 0.33, p = 0.03), respectively. Thus, rats that exhibited greater novelty-induced locomotor behavior also exhibited greater maximum response output for both sucrose and saccharin.

3.3. Pre- and post-diet weight data

Fig. 4A shows that rats divided into the HF and LF diet groups did not differ in weight before the respective diets were given [t(30) = 0.82, p = 0.42]. Following OP/OR grouping based on weight at the end of the 8-week HF diet exposure, pre-diet weights for all groups were analyzed retroactively. Fig. 4B shows that pre-diet weights for LF, OR, and OP rats did not differ [F(2, 21) = 3.09, p = 0.07]. Fig. 4C shows that the weights of the LF, OR, and OP groups all differed from one another after 8-weeks of the LF and HF diet, respectively [F(2, 21) = 13.69, p = 0.0002; Tukey HSD, $p < 0.05$]. Fig. 4D shows that the OP group gained significantly more weight than the LF control and OR group after 8-weeks of diet [F(2, 21) = 11.06, p = 0.0005; Tukey HSD, $p < 0.05$]. As expected, the amount of food eaten (in grams) was significantly correlated with absolute weight (r = 0.91, $p < 0.0001$) and weight gain (r = 0.88, $p < 0.0001$) after 8-weeks of the LF or HF diet (data not shown). Fig. 4E shows that the LF and OP groups ate significantly more food than the OR group [F(2, 21) = 11.89, p = 0.0004; Tukey HSD, $p < 0.05$] from diet start until the end of the 8-week period.

3.4. Pre-diet demand behavior based on post-diet grouping

To assess any group difference in demand behavior before the HF diet was available, pre-diet demand behavior was analyzed based on post-diet grouping. The pre-diet output and demand curves based on the post-diet grouping for sucrose are shown for the OP, OR, and LF groups in Fig. 5A/B. NLME analysis (constant k = 2.50) revealed no significant differences in demand intensity [F(2, 162) = 0.90, p = 0.41] or elasticity [F(2, 162) = 1.99, p = 0.14]. Considering the interest in assessing if weight gain on the HF diet caused changes in demand parameters, linear contrasts for sucrose were performed for only the OP and OR groups. This analysis also revealed no statistical differences in demand intensity [F(1, 162) = 1.69, p = 0.20] or elasticity [F(1, 162) = 2.20, p = 0.14].

The pre-diet output and demand curves based on the post-diet groupings for saccharin are shown for the OP, OR, and LF groups in Fig. 5C/D. NLME analysis (constant k = 2.36) revealed no significant differences in demand intensity [F(2, 161) = 0.90, p = 0.54] or elasticity [F(2, 161) = 0.88, p = 0.42]. Considering the interest in assessing if weight gain on the HF diet caused changes in demand parameters, linear contrasts for saccharin were performed on only the OR and OP groups. This analysis also revealed no statistical differences in demand intensity [F(1, 161) = 1.06, p = 0.30] or elasticity [F(1, 161) = 0.67, p = 0.42].

3.5. Post-diet demand behavior for sucrose and saccharin

The post-diet sucrose output and demand curves are shown for OP, OR, and LF groups in Fig. 6A/B. NLME analysis (best-fit global k = 2.47) revealed a significant main effect of group on α [F(2, 162) = 6.72, p = 0.001], where the sucrose α for the OP group was significantly smaller than the sucrose α for OR and LF groups.

The post-diet saccharin output and demand curves are shown for OP, OR, and LF groups in Fig. 6C and 6D, respectively. NLME analysis (best-fit global k = 2.44) revealed a significant main effect of group on α for saccharin [F(2, 162) = 3.76, p = 0.02], with decreased α for OP relative to both LF and OR groups. Additionally, there was a significant group effect on Q_0 for saccharin [F(2, 162) = 4.52, p = 0.01], where the saccharin Q_0 for the OP group was significantly greater than Q_0 for the OR group.

In summary, these results suggest that OP rats had decreased demand elasticity (α) for both sucrose and saccharin compared to the LF and OR groups, and OP rats also had increased demand intensity (Q_0) for saccharin compared to the OR group.

3.6. Post-diet behavior correlations

After 8-weeks of exposure to the HF diet, various correlations were conducted using weight gain, NPP, locomotor activity, and demand parameters. Omax values for sucrose and saccharin were calculated from the post-diet output curves ([28,56]; Fig. 6A and 6C). Fig. 7 shows

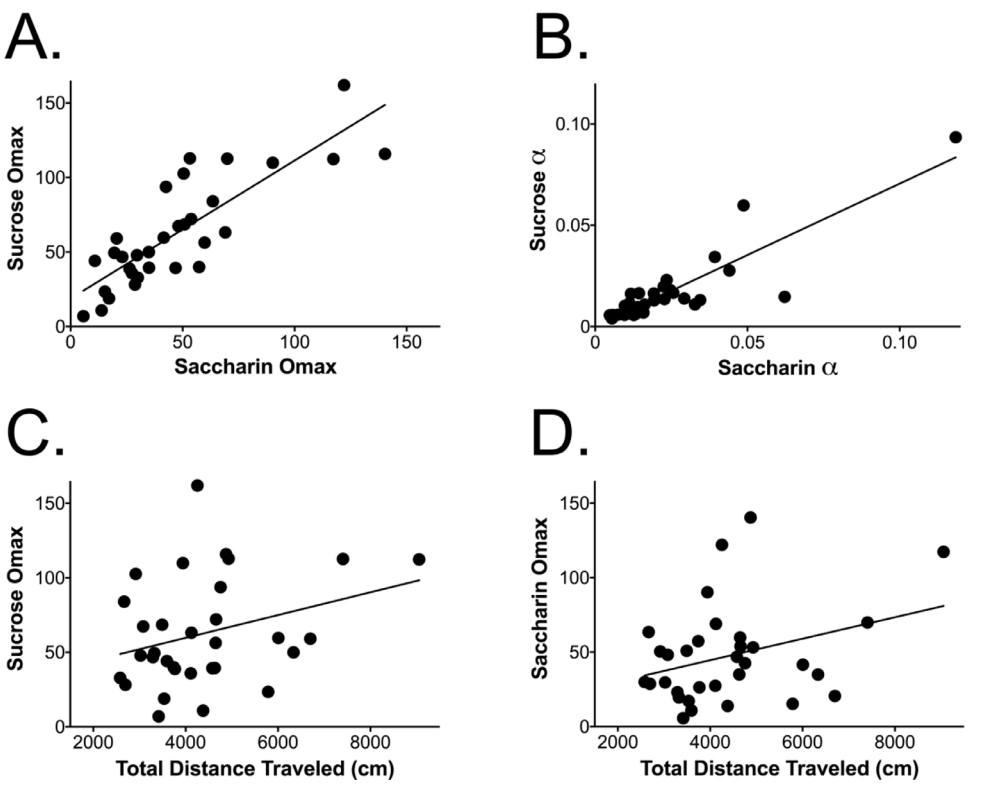

Fig. 3. Pre-Diet Correlations. (A) The maximum output (number of responses) for saccharin was positively correlated with the maximum output for sucrose, $^*p < 0.05$. **(B)** The demand elasticity (α) for saccharin was positively correlated with the elasticity for sucrose, $^*p < 0.05$. **(C)** The total distance traveled during locomotor behavior was positively correlated with the maximum output for sucrose, $^*p < 0.05$. **(D)** The total distance traveled during locomotor behavior was positively correlated with the maximum output for saccharin, $^*p < 0.05$.

that post-diet, the Omax for saccharin was positively correlated with the Omax for sucrose ($r = 0.76$, $p < 0.0001$), suggesting that rats that had greater maximum responses for saccharin also had greater maximum responses for sucrose. No other post-diet correlations were statistically significant. Non-significant correlations included sucrose ($r = 0.037$, $p = 0.86$) and saccharin ($r = 0.017$, $p = 0.94$) Omax correlations with the time spent in the novel side of the NPP chamber, sucrose ($r = 0.11$, $p = 0.61$) and saccharin ($r = 0.042$, $p = 0.85$) Q_0 correlations with the time spent in the novel side of the NPP chamber, sucrose ($r = 0.078$, $p = 0.72$) and saccharin ($r = 0.026$, $p = 0.90$) α correlations with the time spent in the novel side of the NPP chamber, sucrose ($r = 0.06$, $p = 0.80$) and saccharin ($r = 0.15$, $p = 0.48$) Omax correlations with the total distance traveled (cm) in the locomotor chamber, sucrose ($r = 0.036$, $p = 0.87$) and saccharin ($r = 0.17$, $p = 0.43$) Q_0 correlations with the total distance traveled (cm) in the locomotor chamber, sucrose ($r = 0.091$, $p = 0.67$) and saccharin ($r = 0.15$, $p = 0.49$) α correlations with the time spent in the novel side of the NPP chamber, and post-diet weight gain correlations with the total distance traveled (cm) in the locomotor chamber ($r = -0.33$, $p = 0.11$).

4. Discussion

This study is the first to isolate reward-related aspects of obesity using demand analysis in a diet-induced obesity model. Specifically, by using demand analysis, effects of diet, amount of diet eaten, and weight gain on independent facets of reward, namely demand intensity and elasticity, were separated. First, the pre-diet demand results indicated that before the diet, rats had greater demand intensity and decreased elasticity for sucrose compared to saccharin (Fig. 2B). These results suggest that rats, not surprisingly, attributed greater overall value to the caloric reinforcer prior to access to the HF or LF diet. Further, post-diet demand analysis showed that OP rats had decreased elasticity for both sucrose and saccharin compared to OR and LF groups (Fig. 6B and 6D), suggesting significant weight gain on the HF diet (Fig. 4D) drives a higher valuation for both caloric and non-caloric reinforcers. Considering that the amount of food eaten over the 8-week period was the same between the LF and OP groups (see Fig. 4E) this further supports the idea that a HF diet and weight gain, but not necessarily the amount of food eaten, is driving a higher valuation for both reinforcers. OP rats also had greater demand intensity for saccharin compared to the OR group (Fig. 6B), suggesting that significant weight gain as well as the amount of diet eaten (Fig. 4E) affects how much of a non-caloric commodity will be consumed when unconstrained by the cost to procure it. Note, no changes were observed when pre-diet demand behavior was analyzed based on post-diet grouping (see Fig. 5) further supporting the idea that weight gain and a HF diet are driving the changes in demand elasticity while weight gain and amount of diet eaten are driving changes in demand intensity.

Existing evidence suggests that demand intensity is linked to satiety, or the minimum level of consumption that, when reached, will maintain satiety [49]. For example, demand intensity estimates have been coupled to the magnitude of drug reinforcers, tracking drug concentrations in brain [6]. In relation to caloric goods, Hursh et al. [26] found a decrease in demand intensity when two food pellets could be earned per response unit compared to one food pellet, indicating that it took fewer responses at low price points to reach a comparable satiety point. Additionally, obese monkeys respond more for a single caloric food pellet at low price points when compared to controls, suggesting that obesity increases some type of 'satiety threshold' [24,49]. More germane to the current study, Rasmussen et al. [43] found increases in demand intensity (Q_0) in obese Zucker (*fa/fa*) rats responding for sucrose, compared to lean controls. Given the link between demand intensity and satiety, along with the link between satiety and metabolic factors [20], it follows that obesity-induced changes in demand intensity may be the product of some metabolic change. Interestingly, the Rasmussen et al. [43] study lends support to this claim in that the obese Zucker rats utilized are obese because of a genetically-determined leptin deficiency. To the contrary, the current study found no differences in caloric sucrose demand intensity for the OP group, but an increase in non-caloric saccharin demand intensity was found for the OP group relative to the OR rats. Thus, it is possible that the DIO model does not induce

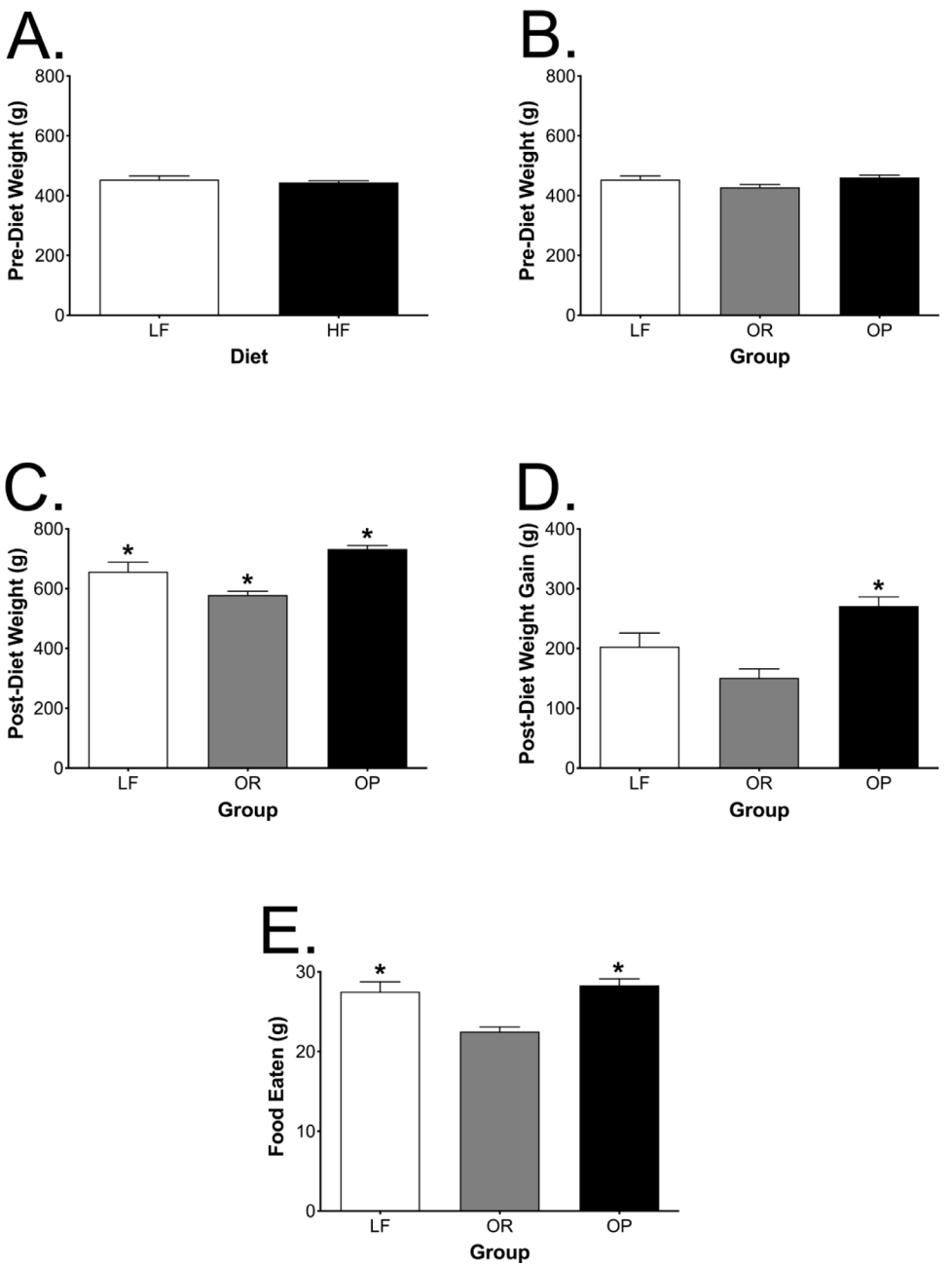

Fig. 4. Pre- and Post-Diet Weight. (A) Rats in the LF (white bars; $n = 8$) and HF (black bars; $n = 24$) groups did not differ in weight before the diet, $p > 0.05$. **(B)** Following OP/OR grouping based on weight at the end of the 8-week HF diet exposure, pre-diet weights in all groups (including LF) were analyzed retroactively ($n = 8$/group); the groups did not differ in weight, $p > 0.05$. **(C)** After 8-weeks of the diet all rat groupings ($n = 8$/group) were significantly different in weight from each other, $^*p < 0.05$. **(D)** After 8-weeks of a high-fat diet OP rats (black bars; $n = 8$) gained more weight than OR (grey bars; $n = 8$) and LF (white bars; $n = 8$) rats, $^*p < 0.05$. **(E)** During the 8-weeks of the LF and HF diet LF (white bars; $n = 8$) and OP (black bars; $n = 8$) rats ate more food than OR (grey bars; $n = 8$) rats, $^*p < 0.05$. All data presented as mean ± SEM.

metabolic changes linked to systematic changes in food-induced satiety. Alternatively, given the changes observed herein in saccharin demand intensity, the link between demand intensity and satiety may not be as strong as previously hypothesized. Alternatively, satiety as a concept may not be strictly constrained to only metabolic processes. While clearly independent and distinct from demand elasticity [19,39], the underlying mechanisms of demand intensity are understudied, leaving a dearth of knowledge regarding the functional relations that govern it. Future research is needed to help establish those relations.

Of note, there are many methodological differences between Rasmussen et al. [42,43] and the current study. The current study used a DIO model thought to better mimic human obesity [33] relative to the leptin receptor deficiency Zucker rat model, a rare cause of human obesity [22]. Further, the current study used liquid sucrose and saccharin, rather than sucrose pellets, and used 10-min sessions that may not have been sufficient time for OP rats to reach the 'satiety threshold' for sucrose, but was sufficient time to reach satiety threshold for saccharin. Additionally, Rasmussen et al. [43] manipulated unit price by increasing the FR requirement and sampled from a larger unit price range. While price effects are theoretically equivalent regardless of manipulation (response requirement or reinforcer magnitude e.g. [8]), recent evidence suggests that these different means of unit price manipulation may have differential effects on demand. For example, rats are more sensitive to unit price changes produced by a decrease in reinforcer magnitude as opposed to an increase in the work required [46].

Generally speaking, while demand intensity has been hypothesized as the ability of a good to sate [6,26], changes in demand elasticity have been proposed to represent changes in the ability of a good to serve as a reinforcer [29]. While Rasmussen et al. [42,43] found that Zucker obese rats exhibited greater demand intensity for a sucrose pellet, they found no difference in demand elasticity compared to lean rats. Interestingly, using the same DIO model as the current study, Brown et al. [12] found no changes in the consumption of palatable food pellets at low price points, but found that on a progressive ratio schedule, OP rats had higher break points for the palatable pellet. Thus, while not directly comparable because reinforcer demand was not assessed, results from

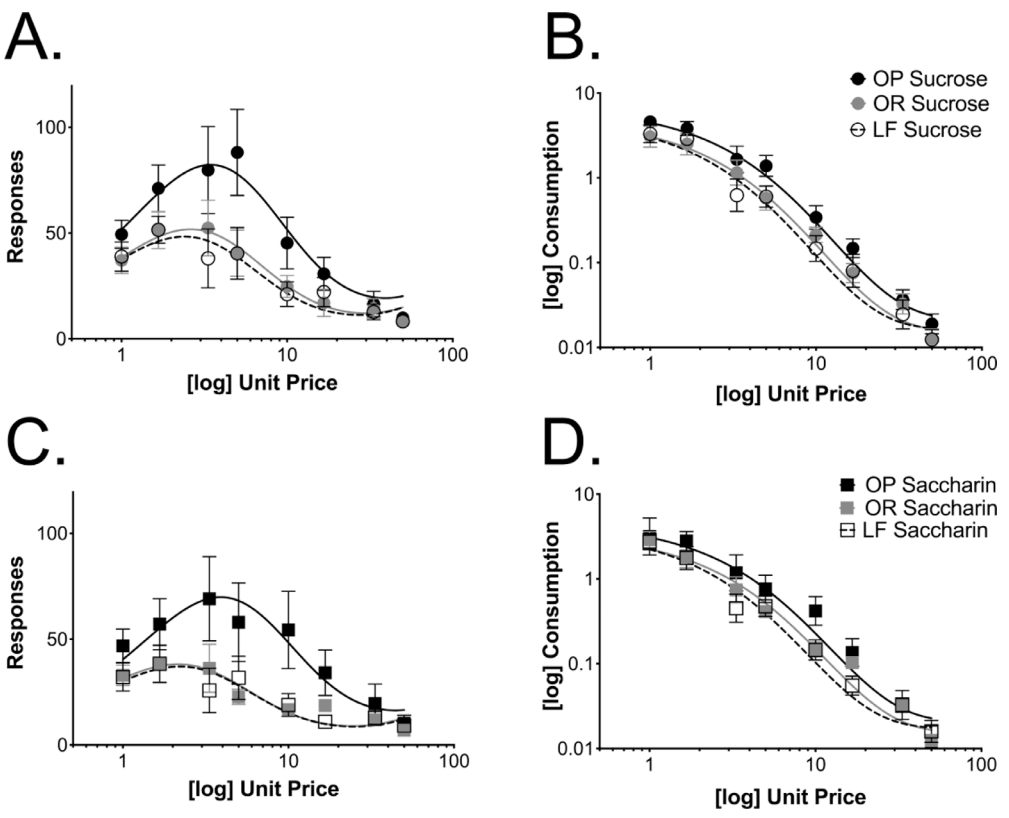

Fig. 5. Pre-Diet Output and Demand Curves Based on Post-Diet Grouping. (A) The maximum output (number of responses) for sucrose was greatest for the OP group (black circles; $n = 8$) compared to the OR (grey circles; $n = 8$) and LF (white circles; $n = 8$) groups. Data presented as mean ± SEM. **(B)** There were no statistical differences in sucrose demand intensity (Q_0) or elasticity (α) between the LF ($Q_0 = 5.36$; $\alpha = 0.020$), OR ($Q_0 = 5.06$; $\alpha = 0.018$), and OP ($Q_0 = 6.93$; $\alpha = 0.011$) groups, $p > 0.05$. Data presented as Log mean ± SEM. **(C)** The maximum output (number of responses) for saccharin was greatest for the OP group (black squares; $n = 8$) compared to the OR (grey squares; $n = 8$) and LF (white squares; $n = 8$) groups. Data presented as mean ± SEM. **(D)** There were no statistical differences in saccharin demand intensity (Q_0) or elasticity (α) between the LF ($Q_0 = 3.96$; $\alpha = 0.028$), OR ($Q_0 = 3.52$; $\alpha = 0.025$) and OP ($Q_0 = 4.74$; $\alpha = 0.017$) groups, $p > 0.05$. Data presented as Log mean ± SEM. In both figures, data points represent average behavior. For output curves, smooth lines represent drawn output functions via NLME-determined demand model parameters of best fit. For the demand curves, smooth lines represent NLME-determined models of best fit.

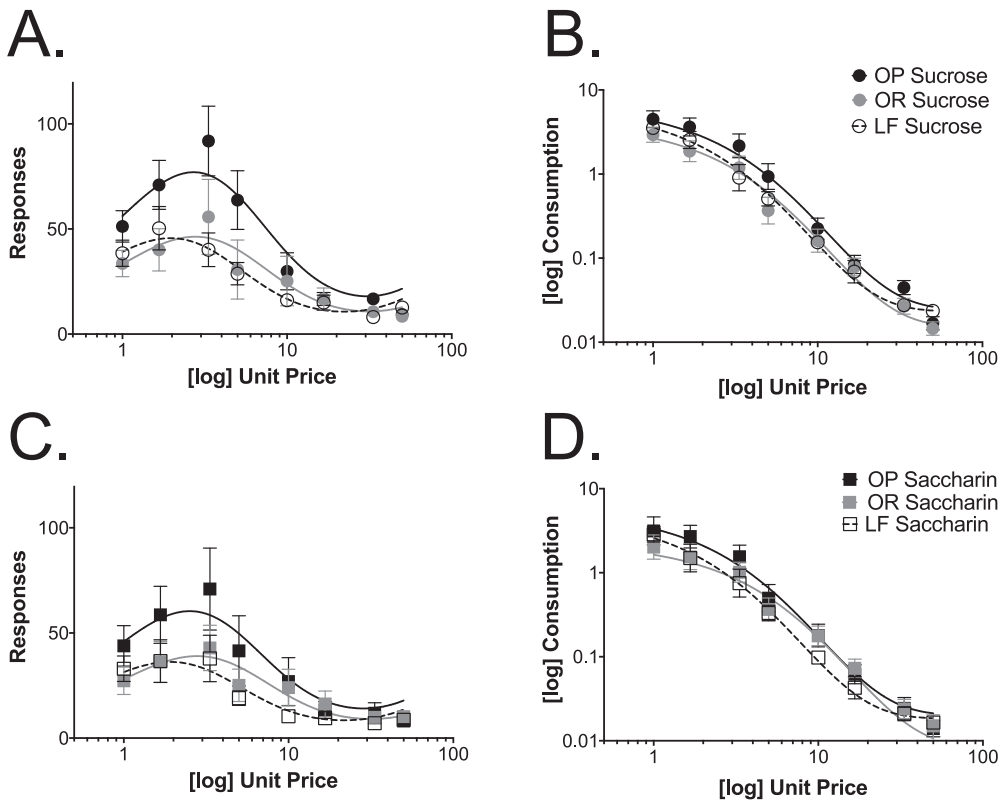

Fig. 6. Post-Diet Output and Demand Curves. (A) The maximum output (number of responses) for sucrose was greatest for the OP group (black circles; Omax = 66.83; $n = 8$) compared to the OR (grey circles; Omax = 46.63; $n = 8$) and LF (white circles; Omax = 46.18; $n = 8$) groups. Data presented as mean ± SEM. **(B)** Sucrose elasticity (α) for the OP group ($\alpha = 0.011$) was decreased compared to the OR ($\alpha = 0.019$) and LF ($\alpha = 0.018$) groups, $^*p < 0.05$. Data presented as Log mean ± SEM. **(C)** The maximum output (number of responses) for saccharin was greatest for the OP group (black squares; Omax = 43.75; $n = 8$) compared to the OR (grey squares; Omax = 40.62; $n = 8$) and LF (white squares; Omax = 32.63; $n = 8$) groups. Data presented as mean ± SEM. **(D)** Saccharin elasticity (α) for the OP group ($\alpha = 0.018$) was decreased compared to the OR ($\alpha = 0.024$) and LF ($\alpha = 0.025$) groups. Demand intensity (Q_0) for the OP group ($Q_0 = 4.77$) was greater than the demand intensity for the OR group ($Q_0 = 2.46$), but not the LF group ($Q_0 = 5.07$), $^*p < 0.05$. Data presented as Log mean ± SEM. In both figures, data points represent average behavior. For output curves, smooth lines represent drawn output functions via NLME-determined demand model parameters of best fit. For demand curves, smooth lines represent NLME-determined models of best fit.

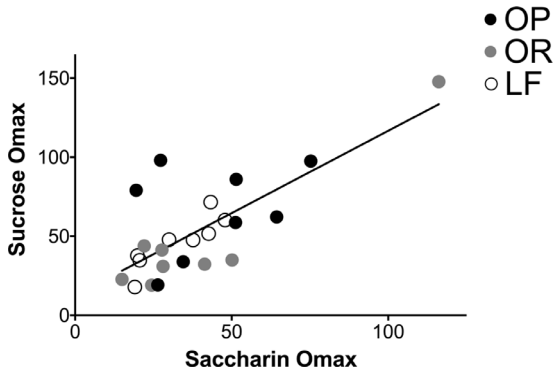

Fig. 7. Post-Diet Demand Correlations. The post-diet maximum output (number of responses) for saccharin was positively correlated with the post-diet maximum output (number of responses) for sucrose, $*p < 0.05$. White circles = LF; Grey circles = OR; Black circles = OP; $N = 24$ (8 rats/group).

Brown et al. [12] are consistent with the current results. Further, in Brown et al. [12] OP rats also consumed more HF diet than OR rats as was found in this study; however, here increased HF diet consumption was only associated with demand intensity changes with saccharin. Thus, the current study extends the findings of Brown et al. [12] to a non-caloric reinforcer and shows that saccharin demand intensity was increased and elasticity decreased in OP rats; this result illustrates how diet type, amount of diet eaten, and weight gain can affect demand specifically. When compared to the Rasmussen [42,43] results using Zucker rats, both Brown et al. [12] and the current results suggest that DIO obesity-induced changes in food-related behavior may not be linked strictly to metabolic changes, but produce important changes in reward processes.

A myriad of evidence suggests that dopamine signaling in the mesocorticolimbic system is related to reward processing, including that related to food reward (e.g. [11,16,44]). Also, some evidence indicates changes in reward processing by DIO (e.g. [38,52]). For example, rodent DIO models have revealed that OP rats exhibit lower D2 receptor density, a neurobiological condition shared with substance use disorder [52], as well as lower dopamine transporter (DAT) expression and function compared to OR rats [38]. Further, OP rats also have lower D1 receptor expression compared to OR rats [1]. High-fat diet and associated weight gain also contribute to decreased dopamine release in the nucleus accumbens [21]. Interestingly, Brown et al. [12] found 'addiction-like' reward changes in glutamate signaling within the nucleus accumbens in OP rats compared to OR rats. Considering that glutamatergic cell signaling can regulate dopamine neurons [36], these glutamatergic changes also could be indicative of differences in OP and OR reward processing. Importantly, neurobiological signaling is not linked to reward uniformly. For example, DAT knockout mice illustrate no changes in food consumption when there is no acquisition cost, but show large changes as the price for food consumption accumulates (see [7] for a discussion). Thus, the aforementioned DAT study shows how dopamine signaling affects the two independent components of reward indexed by demand analysis (i.e., demand intensity and elasticity). As such, demand analysis will help the future opportunity to better isolate specific neurobiological changes to specific reward-related processes.

Evidence is mixed on how sucrose and saccharin affect the dopamine system. For example, D1 antagonism was shown to decrease sucrose- and saccharin-seeking behavior in rats [2,23]. However, sucrose and saccharin cues have differential effects on dopamine signaling [34]. Thus, considering that differences in the dopamine system are observed in OP and OR rats and that sucrose and saccharin may have differential effects on this system, it is possible that an interaction between the DIO model and these two reinforcers could account for the results observed in the current study. Unfortunately, there is a paucity of research assessing how sucrose and saccharin directly affect dopamine signaling in the DIO model.

Importantly, the current results highlight the ubiquitous changes in gustatory reinforcers generally due to HF diet, amount of diet consumed, and weight gain. Rats in this study were given two diets that consisted of either high or low fat content; however, the diets also differed in carbohydrate content (with the HF diet having a lower carbohydrate content than the LF diet). Considering this additional difference in diet, the hypothesis may have been that rats on the LF diet may have a higher demand for sucrose (a carbohydrate) and perhaps saccharin due to the higher level of carbohydrate in the LF diet. However, this did not occur. Thus, exposure specifically to a HF diet coupled with the amount of diet eaten and weight gain resulted in differences in demand parameters for sucrose (carbohydrate) and saccharin, suggesting that changes in overall reward processing occurred and not just a change specific to a given commodity. This is similar to previous results showing that a HF diet can disrupt the acquisition to cocaine self-administration [54] and can reduce amphetamine conditioned place preference [17]. Considering that a HF diet disrupted drug-related behavior suggests that a HF diet can change reward processing in general and not just in a specific fashion (i.e., changes reward related behavior to many commodities and not only for HF food).

Because novelty seeking is associated with 'addiction-like' reward changes [40,50], all animals were screened prior to diet exposure in both novelty-induced locomotor activity and NPP, two independent preclinical measures of novelty seeking [9,15]. Consistent with the established relationship between novelty and reward [3], we found that pre-diet locomotor activity was correlated positively with pre-diet Omax values for sucrose and saccharin (Fig. 3C/D). Yet, pre-diet novelty seeking had no relationship with weight gain or post-diet behavior, suggesting that novelty seeking is not predictive of an obese state or its functional consequences; this result is counterintuitive to findings from the substance use disorder literature [15,50,52]. However, the vast majority of research connecting obesity to substance use disorder has been performed in humans or animals that have been tested after becoming obese. Thus, perhaps the obese state and chronic use of drugs of abuse produce similar biological states, rather than sharing common pre-existing vulnerabilities to the development of each pathology. Overall, the relationship between novelty seeking and obesity is currently unclear.

Important to translational interpretation, the current demand results also show similarities to recent human obesity studies. For example, Epstein et al. [19] found that demand intensity was greater and elasticity decreased for low-density energy foods compared to high-density energy foods. If one assumes that sucrose could be considered a high-density energy food relative to saccharin (low-density energy food), then the saccharin results for the OP rats are similar to the previous findings in humans. Conversely, Epstein et al. [19] also found that demand intensity (Q_0) for high-density foods was positively correlated with body mass index. Here, we found no relationship between sucrose or saccharin Q_0 and weight gain. This difference could be due to several reasons. The Epstein et al. [19] study used the food-purchasing task to collect demand data; thus, reinforcers were not actually earned or consumed as in the current study. Further, even though one could think of sucrose as a high-density food relative to saccharin, in reality it is a comparison of a caloric food to a non-caloric food. Thus, methodological differences make comparisons of interpretation difficult. Nevertheless, the increased use of behavioral economic methods and analyses in human obesity studies provide great potential for an improved translational approach to obesity research. Future studies that focus on utilizing comparable methods and demand analyses in both preclinical models and human clinical studies offer a potentially powerful translational bridge between preclinical and clinical research that may help to better identify comparable neurobehavioral mechanisms underlying obesity.

Collectively, the current experiments suggest that, at least in the DIO model, changes in food-related behavior may be linked to changes

in reward processing, specifically in regard to OP rats. Additionally, by using caloric and non-caloric reinforcers, we extended ideas on the theoretical interpretation of demand intensity. Overall, this study illustrates the utility of using demand analysis in obesity research to isolate independent reward-related processes occurring during obesity onset, as well as adds to the growing body of literature on reward-related aspects of obesity.

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

Acknowledgments

This research was funded by a University of Kentucky Internal Research Support grant from the Office of the Vice President for Research. We would also like to thank Josh Lavy and Andrew Edel for their technical assistance.

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