Individual Differences in Behavioral Responses to Palatable Food or to Cholecystokinin Predict Subsequent Diet-Induced Obesity

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Objective: This study investigated whether individual differences in behavioral responses to palatable food and to the satiation signal cholecystokinin (CCK) in outbred chow-maintained Sprague-Dawley rats enabled prediction of individual differences in weight gained after subsequent high-fat/high-sugar diet (HFHSD) maintenance.

Methods: Meal size, meal number, and early dark cycle intake during initial HFHSD exposure were measured, as were early dark cycle sucrose solution and chow intake, chow meal size and meal number, the intake-suppressive effects of 0.5-µg/kg CCK injection, and CCK-induced c-Fos activation in the nucleus tractus solitarius. Subsequently, rats were maintained on an HFHSD for 5 weeks, and weight gain was determined.

Results: Rats that took larger and less frequent meals on the first day of HFHSD exposure, whose early dark cycle intake (HFHSD and sucrose) was larger during initial HFHSD exposure, gained more weight after HFHSD maintenance. Rats with lesser sucrose intake suppression in response to CCK gained more weight after HFHSD maintenance and displayed reduced CCK-induced c-Fos activation in the nucleus tractus solitarius.

Conclusions: Together, these data identify individual differences in behavioral responses to palatable food and to CCK as novel predictors of diet-induced obesity.

Introduction

In humans and rats, long-term consumption of energy-dense diets leads to variability in the magnitude of weight gain. For example, outbred male Sprague-Dawley rats show individual differences in body weight (BW) gain after multi-week, palatable, energy-dense diet maintenance (1,2). Selective breeding of high and low weight gainers over multiple generations amplifies these traits in a fashion reflecting a polygenic pattern of inheritance (2,3). For the rat gaining weight after high-fat/high-sugar diet (HFHSD) maintenance, multiple effects of weight gain itself could contribute to further weight gain. For example, rats on energy-dense diet maintenance are less responsive to the intake-suppressive effects of exogenously administered gastrointestinal (GI) peptides (e.g., cholecystokinin [CCK], glucagon-like peptide 1, and bombesin) (4-6). For this reason, the current experiments sought to determine whether individual differences in behavioral and physiological features of food intake control exist in chow-maintained Sprague-Dawley rats and whether, if identified, such differences could predict the magnitude of HFHSD-induced BW gain.

Food intake and its underlying parameters, including meal size and meal number, are controlled by actions of various energy-availability signals on central nervous system cells and circuits. One such signal, the GI peptide CCK, is of particular interest. CCK is released from intestinal I cells in response to ingestion. It acts on CCK-1 receptors (CCK-1R) expressed on vagal afferent neurons innervating the GI tract that project centrally to caudal nucleus tractus solitarius (NTS) neurons, and activating both inhibits food intake (7,8). Palatable food taste provides a hedonic signal, arising from oral sensors innervated by cranial nerve afferents that synapse on rostral NTS neurons to stimulate food intake (9-11). Although CCK action and responsiveness to hedonic properties of food have been shown, it is unknown whether individual differences in either predict diet-induced obesity (DIO).

Here, we used a rat model of DIO to investigate the hypotheses that individual differences in sensitivity to the effects of (1) CCK-induced satiation and (2) hedonic properties of palatable food on intake and meal parameters exist in chow-maintained Sprague-Dawley rats and whether, if identified, such differences could predict the magnitude of HFHSD-induced BW gain. Overall, our data support the hypotheses and identify individual differences in behavioral responses to palatable food and to CCK-induced suppression of a palatable diet as novel predictors of HFHSD-induced BW gain.

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Methods

Subjects
Adult male Sprague-Dawley rats (250-265 g on arrival; Charles River Laboratories, Wilmington, Massachusetts) were selected for documented BW heterogeneity during HFHSD maintenance (1,2). Upon arrival, rats were individually housed in wire-bottomed hanging cages under a 12-hour light/12-hour dark cycle with ad libitum access to pelleted chow (Laboratory Rodent Diet 5001; LabDiet, St. Louis, Missouri) and water for at least 1 week. All procedures conformed to the institutional standards of the University of Pennsylvania Institutional Animal Care and Use Committee and were consistent with the NIH Guide for the Care and Use of Laboratory Animals.

General experimental procedures
CCK sensitivity procedures were conducted using within-subject, counterbalanced designs, with at least 48 hours intervening between experimental conditions. All correlation analyses were between-subject comparisons. CCK (H-2080; Bachem Americas Inc., Torrance, California) was dissolved in sterile physiologically 0.9% saline (Fisher Scientific, Hampton, New Hampshire) and kept on ice. Drugs were delivered through intraperitoneal (IP) injection (1 mL/kg).

Experiment 1: assessing whether individual differences in feeding responses during initial HFHSD exposure predict HFHSD-induced BW gain
Naive chow-maintained rats (n = 15) were individually housed in a custom automated food intake monitoring system consisting of hanging wire-bottomed cages modified with an access hole to a food cup resting on an electronic scale. Scale output was connected to software (LabVIEW; National Instruments, Austin, Texas) that calculated food intake from changes in cup weight every 10 seconds. The method has been well validated (12,13). After 5-day apparatus habituation with access to powdered Purina 5001 chow (58% carbohydrate/3% sucrose/13% fat), rats were switched to powdered HFHSD (51.4% kilocalories from carbohydrate, 26% kilocalories from sucrose, 32% kilocalories from fat; D12266B; Research Diets, Inc., New Brunswick, New Jersey). Food intake, meal size, and meal number were measured for the first 2 days of HFHSD access. Three rats left excessive spillage, impairing accuracy of food intake measurements; thus, final analyses included n = 12 of 15 rats. Measurement of HFHSD intake ended after exposure day 2. Subsequently, rats were shifted to 5-week HFHSD maintenance with BW measured weekly.

Experiments 2a and 2b: assessing whether (1) individual differences in CCK-induced intake suppression and (2) baseline intake of sucrose and chow predict HFHSD-induced BW gain

**CCK behavioral sensitivity procedures.** Two experiments in separate groups of rats were conducted to assess CCK’s intake-suppression effects. For one, CCK’s intake inhibitory effects were measured in rats consuming 15% sucrose solution as described previously (14,15), and for the other, CCK’s intake inhibitory effects were measured in rats consuming chow.

**Sucrose.** Naive rats (n = 20) were habituated to home-cage access to 15% sucrose solution (referred to as sucrose going forward) for up to 1 week to reach intake stability within 15% of average response for three consecutive days. Rats were also habituated every other day to IP 0.9% saline. Rats were then subjected to a four-condition counterbalanced experiment in which 0, 0.1-µg/kg, 0.5-µg/kg, or 2.0-µg/kg CCK was administered immediately before dark onset and sucrose intake was measured every 15 minutes for 1 hour after dark onset. The Chow maintenance diet was withheld 2 hours prior to dark onset to limit gastric content variability.

**Chow.** Another group of naive rats (n = 20) was habituated to IP 0.9% saline, and on test days, food was withheld for 2 hours prior to dark onset. Rats were injected with 0, 0.5-µg/kg, or 2.0-µg/kg CCK 2 hours after dark onset to ensure high baseline rates of short-term intake, and intake was measured at 30 and 60 minutes.

**CCK sensitivity.** CCK sensitivity was calculated as the percentage of intake suppression from baseline intake. Greater positive values (greater intake suppression) reflect greater CCK sensitivity, and negative values (lesser intake suppression) reflect lesser CCK sensitivity.

After both CCK sensitivity procedures, groups were shifted to 5-week HFHSD maintenance with BW measured weekly. To determine whether CCK sensitivity and sucrose or chow consumption predicted HFHSD-induced BW gain, behavioral CCK sensitivity and 60-minute sucrose or chow intake (from vehicle condition) were correlated with HFHSD-induced BW gain, behavioral CCK sensitivity and 60-minute sucrose or chow intake (from vehicle condition) were correlated with 5-week BW gain. In the sucrose cohort, one rat was water deprived during 5-week BW measurement. Correlation analyses were conducted for n = 19 of 20 rats. In the chow cohort, one rat was ill and another did not eat under any treatment. Correlation analyses were conducted for n = 18 of 20 rats.

Experiment 3: evaluating whether individual differences in chow meal size and meal number predict HFHSD-induced BW gain
Naive rats (n = 15) were individually housed in a custom automated food intake monitoring system and were habituated to the apparatus with access to powdered Laboratory Rodent Diet 5001 (described in experiment 1). Once habituated, meal size and meal number were measured for 4 days. One rat left excessive spillage, impairing accuracy of intake measurements. Final meal analyses included n = 14 of 15 rats. After meal pattern measurement, rats were shifted to 5-week HFHSD maintenance with BW measured weekly.

Experiment 4: assessing whether individual differences in CCK behavioral sensitivity correlate with CCK-induced NTS neuronal activation
A group of naive rats (n = 25) was used to determine whether CCK behavioral sensitivity correlated with CCK-induced NTS neuronal activation using proto-oncogene c-Fos immunoreactivity (IR). Several days after evaluating CCK sensitivity to sucrose (experiment 2a), rats were administered 0.5-µg/kg CCK (n = 20) or 0.9% saline (n = 5), as this was the lowest effective dose when individual differences were observed. Rats were deeply anesthetized and transcardially perfused with 4% paraformaldehyde 90 minutes after injection, a time point producing maximal c-Fos IR (16). Coronal sections (30 µm) were cut using a cryostat and processed for fluorescence microscopy in the NTS at the rostrocaudal level of the area postrema (AP) as described previously (17,18). Briefly, sections were washed with 1% sodium borohydride, blocked in 0.1M phosphate-buffered saline (PBS) with 5% donkey serum (Jackson ImmunoResearch Laboratories, Inc., West Grove, Pennsylvania), and
incubated in goat primary antibodies for c-Fos (1:1,000; sc-53-2-G; Santa Cruz Biotechnology, Inc., Dallas, Texas). After incubation in fluorescent secondary antibodies (Alexa Fluor 594 Donkey Anti-Rabbit IgG; Jackson ImmunoResearch Laboratories), sections were mounted on slides using Fluoro-Gel (Electron Microscopy Sciences, Hatfield, Pennsylvania). Neurons expressing c-Fos were visualized and quantified (Nikon 80i; NIS-Elements AR 3.0; Nikon Instruments Inc., Melville, New York) at 10× and 20× magnification from coronal sections of the caudal brain stem at −14.2, −14 and −13.8 mm from bregma (three sections/rostrocaudal coordinate), according to the stereotaxic atlas of Paxinos and Watson (19). One animal had insufficient numbers of sections for quantification, so analyses included 24 of 25 rats.

Statistical analyses
All analyses were conducted with Prism 8 (GraphPad Software, San Diego, California). Sucrose and chow intake were analyzed by two-way repeated-measures ANOVA for main effects and by Dunnett multiple comparisons test for interaction effects. Changes in plasma CCK were analyzed by paired t tests. Unpaired t tests were used to compare c-Fos-activated neurons under 0 or 0.5 µg/kg CCK. Pearson correlations were used for all correlation analyses, and the Benjamini, Hochberg, and Yekutieli method was used to control false discovery rate (FDR). Alpha levels were set to 0.05 for all analyses.

Results
Experiment 1: individual differences in meal size, meal number, and intake in the first hour of dark phase during initial HFHSD exposure predict HFHSD-induced BW gain
Displayed in Figure 1A, individual differences in average meal size for all meals on day 1 (24 hours) of HFHSD exposure correlated positively with 5-week HFHSD-induced BW gain ($R^{2} = 0.8$, $P = 0.002$, $r^2 = 0.64$). Additionally, individual differences in the average meal number for day 1 of HFHSD exposure (Figure 1B) correlated negatively with BW gain ($R^{2} = -0.73$, $P = 0.007$, $r^2 = 0.54$). Rats that took fewer meals on day 1 also took larger-sized meals ($R^{2} = 0.61$, $P = 0.003$, $r^2 = 0.61$) and, as noted, also gained more weight during HFHSD maintenance. In addition, individual differences in HFHSD intake in the first 60 minutes after dark onset for days 1 and 2 of HFHSD exposure (average of those 2 days) positively correlated with individual differences in 5-week HFHSD-induced BW gain ($R^{2} = 0.68$, $P = 0.02$, $r^2 = 0.46$) (Figure 1C). There was a trend toward a positive correlation between HFHSD intake in the first 60 minutes after dark onset on day 1 of exposure and 5-week BW gain, but this was not statistically significant ($R^{2} = 0.56$, $P = 0.06$, $r^2 = 0.31$) (Figure 1D). Controlling FDR, results in Figure 1A-1C were considered discoveries. BW gain and individual differences in BW gain were observed (average % BW gain = 39%; SD % BW gain = 7%).

Figure 1 Individual differences in HFHSD meal size, meal number, and early dark cycle cumulative intake predict HFHSD-induced BW gain. (A) The 24-hour meal size (on the first day of HFHSD exposure) positively correlated with HFHSD-induced BW gain. (B) The 24-hour meal number (on the first day of HFHSD exposure) negatively correlated with HFHSD-induced BW gain. (C) The 60-minute HFHSD intake (an average of the first 2 days of HFHSD exposure) positively correlated with HFHSD-induced BW gain. (D) The 60-minute HFHSD intake (on the first day of HFHSD exposure) had a trend toward a positive correlation with HFHSD-induced BW gain. HFHSD-induced BW gain was measured as the percentage of BW gained after 5 weeks of HFHSD maintenance (32% kilocalories from fat).
Experiment 2a: individual differences in sensitivity to CCK’s inhibitory effects on sucrose intake and in baseline sucrose intake predict HFHSD-induced BW gain

Peripheral CCK injection reduced sucrose intake dose dependently (Figure 2A). Two-way repeated-measures ANOVA revealed a significant main effect of dose ($F[3]=13.92$, $P<0.001$), a significant main effect of time ($F[3]=53.19$, $P<0.001$), and a significant dose-by-time interaction ($F[3]=3.43$, $P=0.01$). Dunnett multiple comparisons test revealed that at 15 minutes post injection, sucrose intake (in milliliters) under vehicle ($M=12.06$, $SD=2.57$) was significantly different from that under $0.5$-$\mu$g/kg CCK ($M=9.14$ mL, $SD=4.57$) and $2.0$-$\mu$g/kg CCK ($M=5.50$, $SD=4.57$). Additionally, at 30 and 45 minutes post injection, sucrose intake under vehicle ($30: M=13.14$, $SD=3.09$; $45: M=13.55$, $SD=4.57$) was significantly different from intake under $0.5$-$\mu$g/kg CCK ($30: M=10.75$, $SD=3.90$; $45: M=11.78$, $SD=3.74$) and $2.0$-$\mu$g/kg CCK ($30: M=8.84$, $SD=5.35$; $45: M=9.58$, $SD=5.12$). Sixty minutes post injection, sucrose intake under vehicle ($M=14.35$, $SD=3.05$) was significantly different from that under $0.5$-$\mu$g/kg CCK ($M=11.50$, $SD=5.01$). Treatment with $0.1$-$\mu$g/kg CCK did not significantly reduce sucrose intake at any time point compared with vehicle. Pearson correlations revealed that individual differences in CCK-induced suppression (at 30 minutes after $0.5$-$\mu$g/kg CCK injection) negatively correlated with the percentage of BW gain after 5 weeks of HFHSD maintenance ($32\%$ kilocalories from fat). Positive values are greater intake suppression, and negative values are lesser intake suppression. BW gain was measured as the percentage of BW gained after 5 weeks of HFHSD maintenance ($32\%$ kilocalories from fat). * indicates significant differences from vehicle treatment.

Experiment 2b: individual differences in sensitivity to CCK’s suppressive effects on chow intake and in baseline chow intake do not predict HFHSD-induced BW gain

Peripheral CCK injection reduced chow intake dose dependently (Figure 3). Two-way repeated-measures ANOVA revealed a significant main effect of dose ($F[2]=4.03$, $P=0.039$), a significant main effect of time ($F[1]=35.57$, $P<0.001$), and a significant dose-by-time interaction ($F[2]=6.28$, $P=0.01$). Dunnett multiple comparisons test revealed that at 30 minutes post injection, chow intake (in grams) under vehicle ($M=5.27$, $SD=1.48$) was significantly different from that under $0.5$-$\mu$g/kg CCK ($M=3.76$, $SD=2.25$) and $2.0$-$\mu$g/kg CCK ($M=3.48$, $SD=1.79$). There was no significant effect of either dose on intake inhibition at 60 minutes. In contrast to the results above, Pearson correlations showed that individual differences in CCK’s effects on chow intake inhibition ($0.5$-$\mu$g/kg at 30 minutes chosen a priori based on experiment 2a) did not correlate with subsequent HFHSD-induced BW gain ($R[16]=0.36$, $r^2=0.15$, $P=0.13$). There revealed that individual differences in 60-minute sucrose intake under vehicle positively correlated with BW gain (Figure 2D) ($R[17]=0.59$, $P=0.01$, $r^2=0.35$). Controlling FDR, all correlations reported were considered discoveries. Individual differences in 15-minute intake suppression to $0.5$-$\mu$g/kg CCK did not significantly correlate with the percentage of BW gain and were not deemed discoveries after controlling FDR. BW gain and individual differences in BW gain were observed (average % BW gain=$23.4\%$, SD % BW gain=$4\%$).
was no significant correlation between 60-minute chow intake under vehicle treatment and BW gain ($R^{2} = 0.30$, $r^2 = 0.09$, $P = 0.22$). After controlling FDR, correlations reported were not considered discoveries. BW gain and individual differences in BW gain were observed (average % BW gain = 25.6%, SD % BW gain = 5.8%).

Experiment 3: individual differences in chow meal size and in meal number do not predict HFHSD-induced BW gain
As shown in Table 1, individual differences in average meal size and meal number on day 1 of chow measurements did not significantly predict BW gain ($R^{2} = 0.09$, $r^2 = 0.01$, $P = 0.77$ and $R^{2} = 0.02$, $r^2 = 0.0003$, $P = 0.95$, respectively). Controlling FDR, correlations were not considered discoveries. BW gain and individual differences in BW gain were observed (average % BW gain = 29.17%, SD % BW gain = 4.38%).

Experiment 4: individual differences in sensitivity to CCK's suppressive effects of sucrose intake correlate with c-Fos IR in the NTS
Peripheral CCK injection dose-dependently reduced sucrose intake. Two-way repeated-measures ANOVA revealed a significant main effect of dose ($F[3] = 7.40$, $P = 0.001$) and a significant main effect of time ($F[3] = 67.94$, $P < 0.001$) but did not reveal a significant dose-by-time interaction ($F[3] = 1.391$, $P = 0.25$). Dunnett multiple comparisons test was used to determine dose effects, revealing that sucrose intake (in milliliters) under vehicle (M = 12.10, SD = 3.44) was significantly different from that under both 0.5-µg/kg CCK (M = 10.89, SD = 3.21) and 2.0-µg/kg CCK (M = 9.92 SD = 2.92) (Figure 4A). There was no significant difference between sucrose intake under vehicle treatment and under 0.1-µg/kg CCK. Based on experiment 2a, CCK sensitivity at 30 minutes after 0.5-µg/kg treatment was chosen a priori for correlations with c-Fos IR. Treatment with 0.5-µg/kg CCK significantly increased c-Fos IR in the NTS compared with saline ($t[22] = -2.331$, $P = 0.029$). In addition, individual differences in CCK-induced intake suppression positively correlated with individual differences in CCK-induced c-Fos IR in the NTS ($R^{2} = 0.51$, $r^2 = 0.26$) (Figure 4B-4C), revealing that rats with lesser CCK sensitivity had lower CCK-induced c-Fos IR in the NTS, whereas rats with greater CCK sensitivity showed greater CCK-induced c-Fos IR in the NTS.

**Figure 3** CCK dose-dependently reduced chow intake. * indicates significant differences from vehicle treatment.

**TABLE 1** Individual differences in CCK-induced suppression of chow intake, 60-min chow intake, and 24-h average chow meal size and meal number do not predict HFHSD-induced BW gain

| Chow intake measurement | $R$ | $r^2$ | $P$ |
|-------------------------|-----|-------|-----|
| 0.5-µg CCK (30 min)    | 0.36 | 0.13  | 0.15|
| Vehicle (60 min)       | 0.30 | 0.09  | 0.22|
| Meal size (24 h)       | 0.09 | 0.01  | 0.77|
| Meal number (24 h)     | -0.02| 0.00  | 0.95|

**Figure 4** Individual differences in CCK-induced intake suppression of sucrose correlate with individual differences in CCK-induced c-Fos activation in the NTS. (A) CCK dose-dependently reduced sucrose intake. (B) Individual differences in behavioral CCK sensitivity positively correlated with CCK-induced NTS neuronal activation. (C) Representative images of c-Fos IR in rats with greater and lesser CCK sensitivity. CCK-induced intake suppression was measured as the percentage of suppression of intake after injection of 0.5-µg/kg CCK compared with vehicle treatment. Positive values are greater intake suppression, and negative values are lesser intake suppression. Neuronal activation was measured as the total average number of c-Fos immunopositive cells in the NTS at the level of the AP. * indicates significant differences from vehicle treatment. [Colour figure can be viewed at wileyonlinelibrary.com]
Differential sensitivity to CCK’s suppressive effects on sucrose intake that predicted weight gain was separately correlated with differential CCK treatment–driven activation of caudal NTS neurons. Rats with lesser behavioral CCK sensitivity also displayed lesser CCK-driven c-Fos IR in NTS neurons, with the opposite observed for rats showing greater sensitivity. CCK-induced intake inhibition was shown to result from CCK-1R–mediated, vagal afferent excitation and glutamate release that activates caudomedial NTS neurons (20), whose axons project to local caudal brain stem neurons (21,22) and to basal forebrain neurons and circuits whose actions reduce meal size and cumulative food intake (21,23-29). This result suggests that the biological basis of lesser CCK sensitivity in obesity-prone rats might result from lesser CCK-1R expression on vagal afferents, as rats lacking CCK-1R showed reduced CCK treatment–driven c-Fos in the dorsal vagal complex (4).

Recently, de Git et al. identified that differential sensitivity to the intake-suppressive effects of leptin predicted DIO, paralleling the relationship between differential sensitivity to CCK’s effects on sucrose intake and DIO described here (30). Chow-maintained Wistar rats showing lesser sensitivity to leptin’s effects on food intake inhibition gained more BW when later maintained on an energy-dense diet, a finding consistent with data published by Ruffin et al. (31) in Wistar rats and by Levin and Dunn-Meynell (32) in Sprague-Dawley rats using similar paradigms. It is possible that individual differences in behavioral responses to leptin and to CCK, that each predicts DIO, are interrelated. Indeed, many publications have determined that the behavioral actions of leptin depend on its modulation of within-meal satiation signals. Two individual difference factors relating to consumption of palatable, energy-dense foods predicted DIO. Rats that consumed greater amounts of a palatable diet (HFHSD during initial exposure or sucrose) during the first hour of the dark cycle gained more weight after chronic HFHSD maintenance than rats consuming lesser amounts of HFHSD. Relatedly, chow-maintained rats that consumed larger-sized and fewer numbers of meals during their initial day of HFHSD exposure gained more weight during subsequent multi-week HFHSD maintenance, further suggesting that energy-dense, palatable food intake (measured as cumulative intake or meal parameters) is a predictor of DIO. This is consistent with prior work showing that rats consuming larger meals over 9-day high-energy diet exposure exhibited larger changes in adiposity over this time (37). To determine whether these differential responses were specific to palatable food, we tested whether cumulative chow intake during the first hour of the dark cycle predicted subsequent HFHSD-induced BW gain, but we did not find such a relationship. Additionally, 24-hour chow meal size and meal number did not correlate with BW gain. Such evidence suggests that greater responsiveness to palatable, energy-dense food is a preexisting factor that predicts obesity. This is consistent with prior work showing that rats displaying greater cue-triggered approaches to a sucrose cue and to a food cup (38) and rats that work harder to obtain sucrose pellets (39) both gain more weight after HFHSD maintenance.

It is important to note that CCK sensitivity, a predictor of BW gain, was measured as the percentage of suppression of sucrose intake, yet short-term sucrose intake itself predicted DIO. For this reason, we separately evaluated whether individual differences in CCK-induced suppression of chow intake also predicted BW gain, but we did not find a significant correlation. The nonsignificant correlation between CCK sensitivity on chow and BW gain cannot be explained by an absence of individual differences in either. In fact, there was greater variability in CCK-induced suppression of chow intake than of sucrose (SD = 36.7 and 22, respectively), suggesting that individual differences in CCK sensitivity are present regardless of diet type. Additionally, the average percentage of BW gain and variability in the percentage of BW gain were similar for both Chow (M = 25.6, SD = 5.8) and sucrose (M = 23.4, SD = 4.5) groups, suggesting that differences between the two groups in BW gained did not contribute to differential predictive relationships. Together, these data suggest that diet type is the only meaningful difference between the chow and sucrose groups, indicating that CCK sensitivity and responsiveness to a palatable diet interact and might not be independent obesity predictors. Future studies are needed to understand the mechanisms contributing to this interaction.

This study identified individual differences in responsiveness to sensory cues associated with palatable foods affecting intake and meal size and showed that sensitivity to CCK-induced intake inhibition predicted DIO. Rats that were less sensitive to CCK and that consumed more palatable food gained more BW after subsequent 5-week HFHSD maintenance. Humans consuming a high-energy diet also display individual differences in BW gain, and recent evidence suggests that focusing on individual differences among patients with obesity can inform treatment decisions to maximize weight loss. More specifically, Smith and colleagues showed that humans with obesity with higher sweet preference lost significantly more BW after Roux-en-Y gastric bypass than others treated with vertical sleeve gastrectomy (40). Additionally, Acosta et al. identified that patients with obesity and reduced sensitivity to satiety lost more weight in response to phentermine-topiramate.
treatment (41). Thus, higher sweet taste responsiveness and lesser responsiveness to sweetness, which we also identified as predictors of BW outcome in our animal model, can be used to select obese treatment to maximize weight loss in human populations, making our findings clinically relevant.

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