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Effects of limiting access to diets with different composition on binge-like eating

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**EFFECTS OF LIMITING ACCESS TO DIETS WITH DIFFERENT
COMPOSITION ON BINGE-LIKE EATING**

by

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DEDICATION

I would like to dedicate this work to my family and friends who always supported me during my journey to medical school.

ACKNOWLEDGMENTS

I would like to thank Dr. Cottone and Dr. Sabino for their mentorship and the opportunity to learn from and participate in the Laboratory of Addictive Disorders. I would also like to thank Sema Quadir and Margaret Minnig for their assistance throughout my time in the laboratory.

**EFFECTS OF LIMITING ACCESS TO DIETS WITH DIFFERENT
COMPOSITION ON BINGE-LIKE EATING**

HARRISON SUNJOON LEE

ABSTRACT

Binge Eating Disorder (BED) is a deadly, psychiatric condition which affects about 10 million people in the USA. It is characterized by discrete and recurrent binge eating episodes consisting of rapid consumption of excessive amounts of highly palatable, energy-dense food (e.g. rich in sugars and fats) within discrete periods of time. Our laboratory has been focusing on the understanding of the behavioral, metabolic, and neurobiological factors underlying BED, through the development of an animal model of binge-like eating. This model is based on a limited access schedule in which rats are exposed 1-hour/day to a high-sucrose diet (HSD) in operant conditioning self-administration boxes. However, the consummatory and metabolic outcomes of exposing rats to a high-fat diet (HFD) in the same procedure are unknown. The aim of this thesis was to test the consummatory and metabolic effects of 1-hour limited access to either a HSD or a HFD in an operant rat model of binge-like eating. For this purpose, female rats were subjects of the binge-like eating procedure by limiting access to a HSD, a HFD, or a standard Chow diet. Our results show that limiting access to either a HSD or a HFD promoted binge-like eating as compared to control Chow diet. HSD binge-like eating was based on a true increase in the amount of food consumed, that is, an increased eating rate. Such suggests increase in palatability and a decrease in the home-cage standard chow intake, likely due to a negative contrast effect. Conversely, binge-like eating of the high-

fat diet resulted from passive energy consumption due to the high energy-density of the food. Also, HFD binge-like eating was accompanied by neither increased eating rate nor rejection of the home-cage chow. Moreover, while HSD rats consumed less energy than HFD rats, the former were more energy efficient and gained more body weight than the latter. These results provide information on how the quality of food can deeply influence the behavioral and metabolic outcomes of binge-like eating.

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LIST OF ABBREVIATIONS

- BED Binge Eating Disorder
- HFD High Fat Diet
- HSD High Sucrose Diet
- IACUC..... Institutional Animal Care and Use Committee

INTRODUCTION

Binge Eating Disorder: Epidemiology and Diagnostic Criteria

The lifetime prevalence of Binge eating disorder (BED) in the United States is estimated at 2.6% and epidemiological data show that BED, as many other eating disorders, occurs more commonly in women than men (Kessler et al., 2013).

Approximately 79% of people suffering with BED also have other psychiatric disorders; common comorbid psychiatric conditions include: (1) specific phobia (37%), (2) social phobia (32%), (3) post-traumatic stress disorder (26%), and (4) alcohol use disorder.

BED also has medical comorbidities, including obesity, diabetes, and cardiovascular diseases (American Psychiatric Association, 2013; Becker & Grilo, 2015). For more information regarding comorbid diseases and their comorbidity percentages with BED, please refer to **Table 1**.

Table 1. Comorbidity of Binge Eating Disorder with Other Core Disorders. The following table illustrates comorbidity of BED with other disorders among U.S. adults (Merikangas et al., 2010).

Comorbid Disorders	Comorbidity with BED (%)
Anxiety Disorders	65.1
Mood Disorders	46.4
Impulse Control Disorders	43.3
Substance Abuse Disorders	23.3
Any Disorder	78.9

BED was first coded as a separate eating disorder in the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (American Psychiatric Association, 2013). Beforehand, BED was listed among the “Eating Disorders not Otherwise Specified.”

Diagnostically, BED is characterized by discrete and recurrent episodes of binge eating. A binge eating episode involves a rapid consumption of excessive amounts of food within a discrete time period (within 2 hours). Moreover, a binge episode can occur in the absence of hunger and may involve some emotional distresses, such as “a sense of loss of control, disgust, guilt, depression and embarrassment” (American Psychiatric Association, 2013; Corwin & Buda-Levin, 2004; Cottone, Sabino, Steardo, & Zorrilla, 2008b; Yanovski, 2003). DSM-5 states that binge episodes can be associated with at least three of the following criteria: (1) eating much more rapidly than normal, (2) eating until feeling uncomfortably full, (3) eating large amounts of food when not feeling physically hungry, (4) eating alone because of feeling embarrassed by how much one is eating, (5) feeling disgusted with oneself, depressed, or very guilty afterwards (American Psychiatric Association, 2013). For full diagnostic criteria, please refer to **Table 2**.

Table 2. Binge Eating Disorder Diagnostic Criteria. DSM-5 provides diagnostic criteria for binge eating disorder (American Psychiatric Association, 2013).

<p>Binge-Eating Disorder</p> <p>Diagnostic Criteria</p> <p>A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:</p> <ol style="list-style-type: none">1. Eating, in a discrete period of time (e.g., within any 2-hour period) an amount of food that is definitely larger than what most people would eat in a similar period of time under similar circumstances.2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating). <p>B. The binge-eating episodes are associated with three (or more) of the following:</p> <ol style="list-style-type: none">1. Eating much more rapidly than normal.2. Eating until feeling uncomfortably full.3. Eating large amounts of food when not physically feeling hungry.4. Eating alone because of feeling embarrassed by how much one is eating.5. Feeling disgusted with oneself, depressed, or very guilty afterward. <p>C. Marked distress regarding binge eating is present.</p> <p>D. Thine binge eating occurs, on average, at least once a week for 3 months.</p> <p>E. The binge eating is not associated with the recurrent use of inappropriate compensatory behavior as in bulimia nervosa and dose not occur exclusively during the course of bulimia nervosa or anorexia nervosa.</p>
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Animal Models of Binge-like Eating

The use of animal models is a common practice in preclinical research. Animal models enable researchers to use experimental methodologies that could not be used in humans for ethical reasons or for potential harm to subjects. Animal models are also used in the field of psychiatry, but since the diagnosis of mental disorders is based on variables which are difficult to mimic and interpret in animals (e.g. “guilt”, “disgust”, “embarrassment”), this aspect adds a further layer of complexity. Despite these challenges, in the recent years, preclinical animal research on binge eating has exponentially developed, and animal models of binge-like eating have been very useful to gain insights about behavioral and neurobiological factors underlying binge eating.

Animal models of binge eating disorder can be classified into four different categories: (1) etiologic, (2) isomorphic, (3) mechanistic, and (4) predictive. As the cause of human bingeing is unknown, etiological models have not been developed. Isomorphic models are designed to replicate human symptoms of binge eating in animals. Even though animal models cannot be used to measure negative feelings associated with binge eating in humans, valid measures associated with depression, anxiety, stress, and fear can be measured to evaluate bingeing related distress in animal models. Because of the difficulty to operationalize these subjective feelings, in isomorphic models, objective criteria of binge-like eating have been developed. Those criteria include: (1) binge-type eating should occur repeatedly over an extended time, (2) bingeing rats should consume

more food in a short, defined period of time than controls under similar environment, and (3) compensatory behaviors, if present, should be initiated by the animal, not by the investigator. Mechanistic models are designed to investigate neurobiological mechanisms associated with development and maintenance of bingeing . Although few mechanisms have been proposed, the exact neurobiological cause of bingeing is unknown, and hence, no mechanistic models are available. Lastly, predictive models are used to test possible treatments for bingeing -related disorders (Corwin & Buda-Levin, 2004).

Manipulations of experimental variables in model of binge-like eating

In preclinical research, animal models of binge-like eating can be developed through the manipulation of different variables. Here, a description of the most important experimental manipulations used to model binge-like eating follows.

1) Food type

The increased availability of energy-dense “palatable” food is a risk factor for eating disorders and obesity (Hill, Wyatt, Reed, & Peters, 2003). Palatable foods are typically energy-dense foods, rich in sugars or fats and result in increase of daily caloric intake (Bake, Morgan, & Mercer, 2014; Boggiano et al., 2005; Cottone et al., 2008b). Because binges in humans often involve palatable foods, binge-like eating animal models also oftentimes employ highly palatable food (Hagan, Chandler, Wauford, Rybak, & Oswald, 2003; Kales, 1990). Notably, although preclinically the term ‘palatable’ is used by researchers to denote a diet which is generally preferred by animals, this is an

anthropomorphic terminology. Sensory-hedonic stimuli, instead of homeostatic or nutritional values of food, motivate eating and lead to a dysregulation of eating behavior (Oswald, Murdaugh, King, & Boggiano, 2011; Wardle, Guthrie, Sanderson, & Rapoport, 2001).

2) *Schedule of access to palatable food*

As previously discussed, a diagnostic criterion of BED listed in the DSM-V is: “Eating, in a discrete period of time (e.g., within a two hour period), an amount of food that is definitely larger than what most people would eat during a similar period of time and under similar circumstances.” Indeed, in BED, as well as in other eating disorders, binge episodes are not only characterized by eating energy-dense, highly palatable foods, but they also occur very rapidly and in a short period of time. This characteristic has been used for decades in preclinical research to model binge-like eating in animals (Avena, Rada, & Hoebel, 2006; Corwin & Wojnicki, 2006; Cottone et al., 2008b; Micioni Di Bonaventura et al., 2014). This experimental manipulation is typically called “*limited access or intermittent access to palatable food*” and can be as short as 10 minutes a day (Cottone et al., 2008b). Limited access to palatable food procedures often show *escalation of intake* with repeated exposures (Dore et al., 2014; Parylak, Cottone, Sabino, Rice, & Zorrilla, 2012; Spierling et al., 2018; Velazquez-Sanchez et al., 2015), a characteristic that is considered a hallmark of addiction (Ahmed & Koob, 1998; Ahmed, Walker, & Koob, 2000). Furthermore, providing a highly palatable diet under a limited access protocol not only helps develop overeating of the palatable diet, but also induces

undereating of the less preferred alternative (i.e. standard laboratory chow diet).

3) *Food restriction/deprivation*

Another important risk factor for obesity and eating disorders is dieting (Dulloo & Montani, 2015; Herman & Polivy, 1990; Lowe, Doshi, Katterman, & Feig, 2013; Stice, Davis, Miller, & Marti, 2008). Indeed, food restriction/deprivation has been used for decades in preclinical research to induce overeating in animals (Avena et al., 2006; Corwin & Wojnicki, 2006; Cottone et al., 2008b; Micioni Di Bonaventura et al., 2014). It is important to note that while both food restriction/deprivation and exposure to highly palatable food induce overeating/binge eating, the two experimental manipulations induce profoundly different behavioral, neurobiological and pharmacological processes (Cottone, Sabino, Steardo, & Zorrilla, 2009; Cottone et al., 2012; Smith et al., 2015b): on one hand, food restriction/deprivation causes deficits in energy intake, which promotes greater consumption of food also as an energy-homeostatic response; on the other hand, exposure to highly palatable food over-activates reward neurocircuitries and produces overeating through hedonic mechanisms (Cottone, Sabino, Steardo, & Zorrilla, 2008a; Ferragud et al., 2017; Smith et al., 2015a).

4) *Stress*

In humans, stress can affect food intake bidirectionally: following a stressful event, some people tend to undereat, others tend to overeat (Adam & Epel, 2007). Importantly, in individuals affected by eating disorders, stress can trigger binge eating (Greeno &

Wing, 1994; Heatherton, Herman, & Polivy, 1991). Stress is, therefore, used in preclinical research as a variable to affect feeding. Similar to humans, while stress is generally anorectic in animals (Hotta, Shibasaki, Arai, & Demura, 1999; Valles, Marti, Garcia, & Armario, 2000), following a history of aberrant feeding behavior, stress can instead trigger binge-like eating (Calvez & Timofeeva, 2016; Hagan et al., 2002; Micioni Di Bonaventura et al., 2014).

Operant rat model of binge-like eating

In the past years, our laboratory has developed, validated and characterized an isomorphic model of operant rat model of binge-like eating with limited access to highly palatable food (Blasio, Steardo, Sabino, & Cottone, 2014; Cottone et al., 2012; Ferragud et al., 2017; Moore, Blasio, Sabino, & Cottone, 2018; Smith et al., 2015a; Velazquez-Sanchez et al., 2014; Velazquez-Sanchez et al., 2015). This operant rat model of binge-like eating involves 1-hour daily sessions of limited access to a highly palatable, sucrose diet (Blasio, Rice, Sabino, & Cottone, 2014; Cottone et al., 2012; Velazquez-Sanchez et al., 2014). During the 1-hour daily session, rats poke their nose through a swinging door and receive food whose presentation is paired with an overhead light cue.

In the latest decade, by using this animal model our laboratory has shown that rats undergoing the operant binge-like eating procedure exhibit several binge-related behaviors, such as (1) excessive food intake in a short period of time, (2) loss of control over feeding, (3) increased conditioned food reward, and (4) increased food seeking

behavior. Hence, this operant rat model of binge-like eating can develop a “multi-symptomatic” phenotype (Blasio, Steardo, et al., 2014; Cottone et al., 2012; Ferragud et al., 2017; Moore et al., 2018; Smith et al., 2015a; Velazquez-Sanchez et al., 2014; Velazquez-Sanchez et al., 2015).

Still, since the development of the operant rat model of binge-like eating only a single highly palatable diet has been used. This diet is a sucrose-rich food, which is highly preferred by rats when compared to the standard chow diet (Cottone et al., 2008a). Therefore, it is unknown what the effects of a different highly palatable fat-rich diet would be in the operant rat model of binge-like eating. Hence, the aim of this thesis was to compare the known effects of a high-sucrose to the effects of a high-fat diet on the operant rat model of binge-like eating.

Aim of the Study

To test the consummatory and metabolic effects of 1-hour limited access to a high-sucrose diet (HSD) and a high-fat diet (HFD) in an operant rat model of binge-like eating.

MATERIALS AND METHODS

Subjects

Female Sprague Dawley Rats (n=30), (45 days old from Charles River, Wilmington, MA) weighing 170-220 grams upon arrival, were single housed in wire-topped, plastic cages (27x48x20cm). Rats were housed in a 12/12 hours reverse light cycle (lights off at 11am) and in a humidity- and temperature-controlled vivarium. Rats had access to corn-based chow (Harlan LM-485 Diet 7012 (65% (kcal) carbohydrate, 13% fat, 21% protein, 3.1 kcal/g); Harlan, Indianapolis, IN) and water *ad libitum* in their home cage. All procedures of the experiment adhered to the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by Boston University Institutional Animal Care and Use Committee (IACUC).

Table 3. Diets' composition. Macronutrient composition of the diets used in this study: Chow (TestDiet, 5TUM diet), high sucrose diet (TestDiet, 5TUL), and high fat diet (Bio-Serv, F07679).

	Chow	HSD	HFD
Manufacturer	TestDiet	TestDiet	Bio-Serv
Macronutrient composition	Kcal %	Kcal %	Kcal %
Protein	24.1	20.6	15
Carbohydrate	65.5	66.7	25
Fat	10.4	12.7	60
kcal/g	3.30	3.44	5.23

Apparatus for Self-Administration Procedures

Self-administration procedures were conducted in operant test chambers (30x24x29cm) (Med Associates Inc., St. Albans, VT). Each operant test chamber had a stainless-steel grid floor and was located inside ventilated, sound-attenuating enclosures (66x56x36cm) (Blasio, Rice, et al., 2014; Cottone et al., 2012). Pellet dispensers delivered food reinforcers (45 mg pellets), and solenoids delivered water reinforcers (0.1 ml water) into liquid cup nose-poke receptacles, which were adjacent to pellet receptacles. 28-V stimulus cue-lights were located above each lever and above the food magazine. Light cues (lasting 0.5 sec) were paired with the delivery of pellets and water. All responses were recorded by automatically by microcomputer with 10 msec resolution.

Operant Binge-like Eating Procedure in *Ad Libitum* Fed Rats

Training: One day after arrival, rats were provided an AIN-76A-based diet as home-cage diet. Hereafter, the AIN-76A-based diet would be referred to as ‘Chow’ (TestDiet, 5TUM diet formulated as 4–5 g extruded pellets (65.5% (kcal) carbohydrate, 10.4% fat, 24.1% protein, 3.3 kcal/g); Richmond, IN, see **Table 3**). As previously described (Blasio, Rice, et al., 2014; Cottone et al., 2012; Velazquez-Sanchez et al., 2014), rats were trained to self-administer AIN-76A -based 45 mg precision food pellets (Chow) and water (0.1ml) under a Fixed Ratio 1 (FR1) schedule of reinforcement in the operant chambers. During these training sessions, the 45 mg pellets had identical

composition as the home-cage diet (Chow). Food composition was kept same in order to ensure that food intake during operant sessions was influenced only by homeostatic needs, not by any hedonic factors (Blasio, Rice, et al., 2014; Cottone et al., 2012). Daily operant 1-hour session took place 1–2 hours before the dark cycle onset.

Testing: After establishing stable baseline performance in the daily 1-hour FR1 sessions, rats were matched for their body weight, daily food intake, feed efficiency, water and food responding in the sessions, and they were subdivided into three experimental groups: One set (10 rats) was assigned to a Chow group and received the same 45mg pellets received in the training phase. A second set (10 rats) was assigned to a HSD group and received 45mg pellets that were composed of nutritionally complete, chocolate-flavored, high-sucrose AIN-76A-based diet. This sucrose diet was comparable in macronutrient composition and energy density to the chow diet (TestDiet, chocolate flavored 5TUL diet formulated as 45 mg precision food pellets (66.7% (kcal) carbohydrate, 12.7% fat, 20.6% protein, 3.44 kcal/g); Richmond, IN, **Table 2**); previous experiments have demonstrated that all rats strongly prefer this chocolate-flavored diet (Cottone et al., 2008a; Cottone, Sabino, Steardo, et al., 2009). A third set (10 rats) was assigned to a HFD group and received 45 mg pellets with the following composition: Bio-Serv, F07679 diet formulated as 45 mg precision food pellets (25% (kcal) carbohydrate, 60% fat, 15% protein, 5.23 kcal/g); Flemington, NJ, **Table 2**. Subjects were tested daily and were never food restricted/deprived.

Rate of Sustained Eating: Inter Food Interval (IFI) Analysis

The analysis of the ln-transformed duration of consecutive (uninterrupted by drinking) Inter Food Intervals (IFI) was performed to study differences in rate of sustained eating among the three experimental groups (Chow vs. Palatable vs. HFD) (Cottone et al., 2012). IFI is inversely related to eating rate and, therefore, significant decreases in IFI indicate an increased eating rate. Moreover, similar to licking rate, IFI has been operationalized as a validated measure that is inversely related to palatability, where significant decreases in IFI indicate an increased eating rate (Cottone et al., 2008a).

Home-cage Food Intake, and Body Weights

23-hour home-cage food intake (g) and body weights (g) of subjects were measured daily before each 1-hour self-administration session. 23-hour home-cage food intake was calculated as the food consumed between the end of a self-administration session and the beginning of the next one. Kcal values were calculated by multiplying the values in grams by the caloric density of the different diets (3.3 kcal/g for Chow, 3.44 for HSD, and 5.23 for HFD). Daily 24-hour food intake (kcal) was calculated as the sum of the 23-hour home-cage food intake (kcal) and 1-hour food intake self-administered into the operant chambers (kcal). Cumulative 1-hour food intake in g and kcal were calculated as the sum of the individual 1-hour food intake in g and kcal respectively throughout the

21 days of study. Cumulative body weight gain at any given day was calculated as the body weight gained between the beginning of the self-administration testing and that certain day. Cumulative food intake (kcal) was calculated as the sum of daily 24-hour food intake (kcal). Average and cumulative feed efficiency was calculated as body weight change (mg) gained in a certain period of time divided by the food intake (kcal) in the same period (Dore et al., 2014).

Statistical Analysis

1-hour food intake (g), 1-hour food intake (kcal), 24-hour food intake (kcal), 23-hour food intake (kcal), cumulative body weight gain (g), IFI (Ln(sec)), cumulative food intake (kcal), and feed efficiency (mg/kcal) during the 21 days of self-administration were analyzed using two-way analyses of variance (ANOVAs) with Diet as a between-subjects factor and Day as a within-subject factor. Cumulative 1-hour food intake (g), and Cumulative 1-hour food intake (kcal) were analyzed using one-way ANOVAs with Diet as a between-subjects factor. Fisher's Least Significant Difference test was used to interpret significant group differences.

The software packages used were SigmaPlot 14.0 (Systat Software, Inc., Point Richmond, CA), Statistica 12.0 (StatSoft, Tulsa, OK).

RESULTS

Effects of 1-hour Limited Access to Diets with Different Macronutrient Composition on Binge-like Eating

1-hour food intake (g). As shown in **Figure 1**, the statistical analysis of the quantity of grams of food ingested during the 1-hour self-administration sessions revealed a significant main effect of DIET (Diet: $F(2,27)=7.05, p<0.01$) a significant main effect of DAY (Day: $F(20,540)=8.84, p<0.001$) and a significant interaction DIET*DAY (Diet X Day: $F(40,540)=2.85, p<0.001$).

As expected, the intake in grams of Chow control rats remained stable and steady throughout the entire period of study. Unexpectedly, the intake of HFD rats did not reliably increase across the 21 days, except for a couple of days (15th and 16th) in which it differed from Chow control intake. Instead, the grams of food ingested by HSD rats escalated slowly, doubling towards the end of the 3-week window. Indeed, starting from day 3 HSD rats started eating more grams of food as compared to both Chow and HFD rats. The escalated intake of HSD rats resulted in an overall larger amount of food in grams as compared to both Chow and HFD throughout the entire study (Diet: $F(2,27)=7.05, p<0.01$; **Figure 2**).

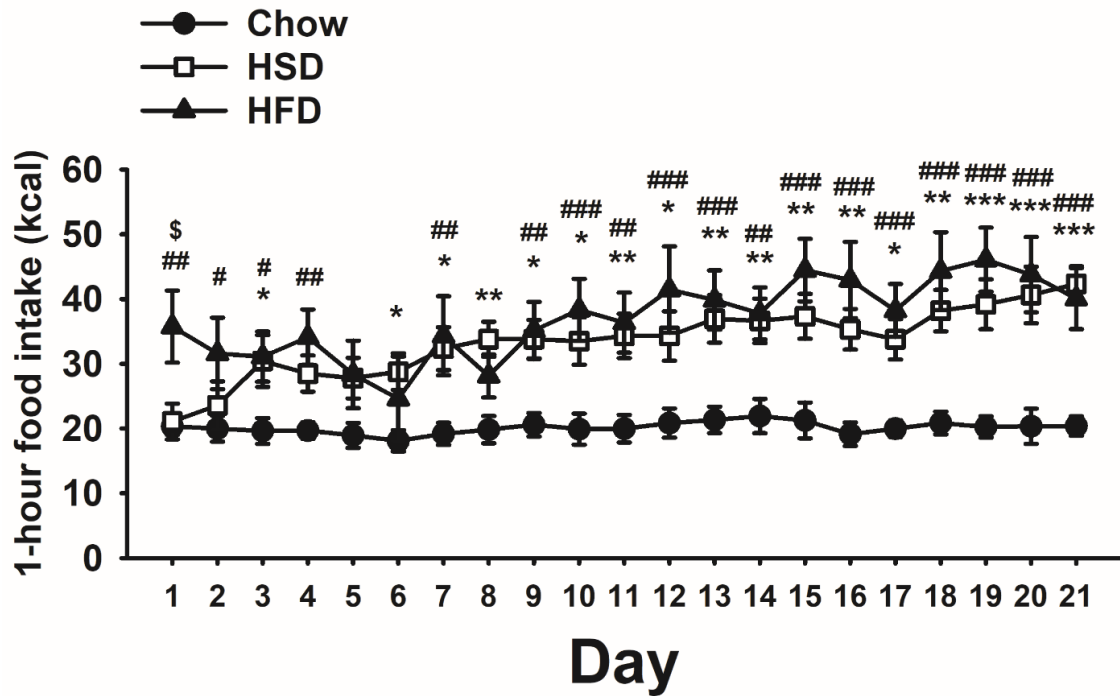


Figure 1. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on food intake (g) in female Sprague Dawley rats ($n=10/\text{group}$). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M\pm\text{SEM}$. Symbols denote: * HSD differs from Chow, $p<0.05$, ** $p<0.01$, *** $p<0.001$; # HFD differs from Chow, $p<0.05$, ## $p<0.01$, ### $p<0.001$; \$ HSD differs from HFD, $p<0.05$, \$\$ $p<0.01$, \$\$\$ $p<0.001$ (Fisher's Least Significant Difference (LSD) test).

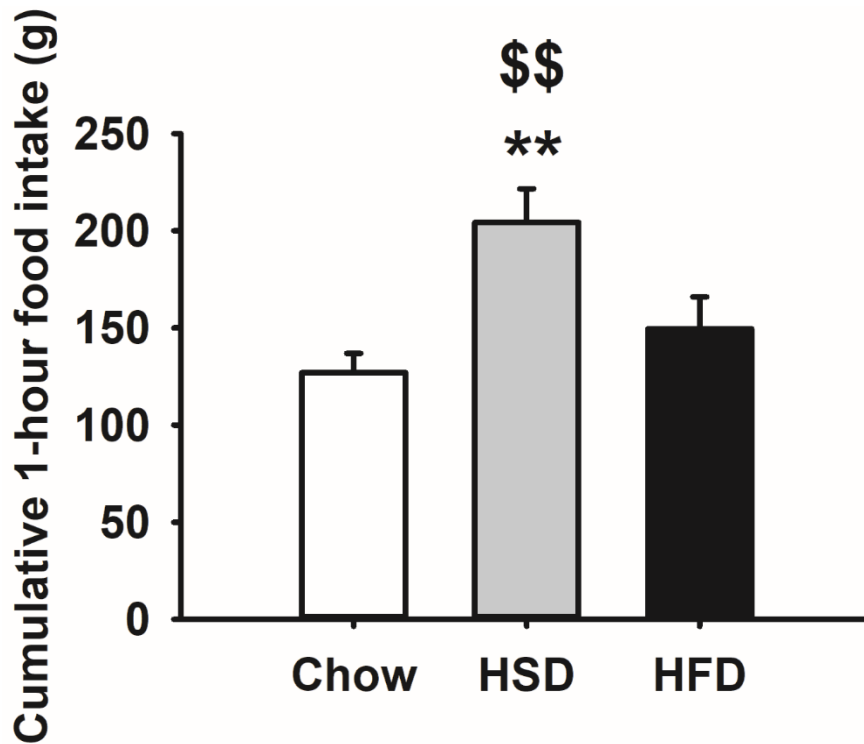


Figure 2. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on cumulative 1-hour food intake (g) in female Sprague Dawley rats ($n=10/\text{group}$). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M \pm \text{SEM}$. Symbols denote: ** HSD differs from Chow, $p < 0.01$; \$\$ HSD differs from HFD, $p < 0.01$ (Fisher's Least Significant Difference (LSD) test).

1-hour food intake (kcal). As shown in **Figure 3**, the statistical analysis of the energy (kcal) of food consumed during the 1-hour self-administration sessions, revealed a significant main effect of DIET (Diet: $F(2,27)=9.17, p<0.001$), a significant main effect of DAY (Day: $F(20,540)=7.20, p<0.001$), and a significant interaction DIET*DAY (Diet X Day: $F(40,540)=2.33, p<0.001$).

Consistently with the grams of food ingested, Chow control rats showed a steady energy consumption throughout the entire period of study. Moreover, given the similar energy density of the sugary diet as compared to the standard chow diet (3.44 vs 3.3 kcal/g, respectively), consistently with the grams of food ingested, HSD rats escalated and doubled their energy consumption as compared to Chow controls. Although the grams of food ingested were the same, since the high fat diet was more energy dense than both the sugary and the standard chow diets, the energy consumption of HFD rats was higher than any other experimental group already on day 1. While the intake of HFD rats remained steadily higher than Chow rats throughout the 21 days of observation, given the escalation of HSD rats, the difference between HFD and HSD kcal consumed disappeared quickly. Despite the grams of food consumed, the passive intake of rats ingesting the high fat diet was higher than the cumulative intake of control Chow rats, but equivalent to the cumulative intake of HSD rats (Diet: $F(2,27)=9.17, p<0.001$; **Figure 4**).

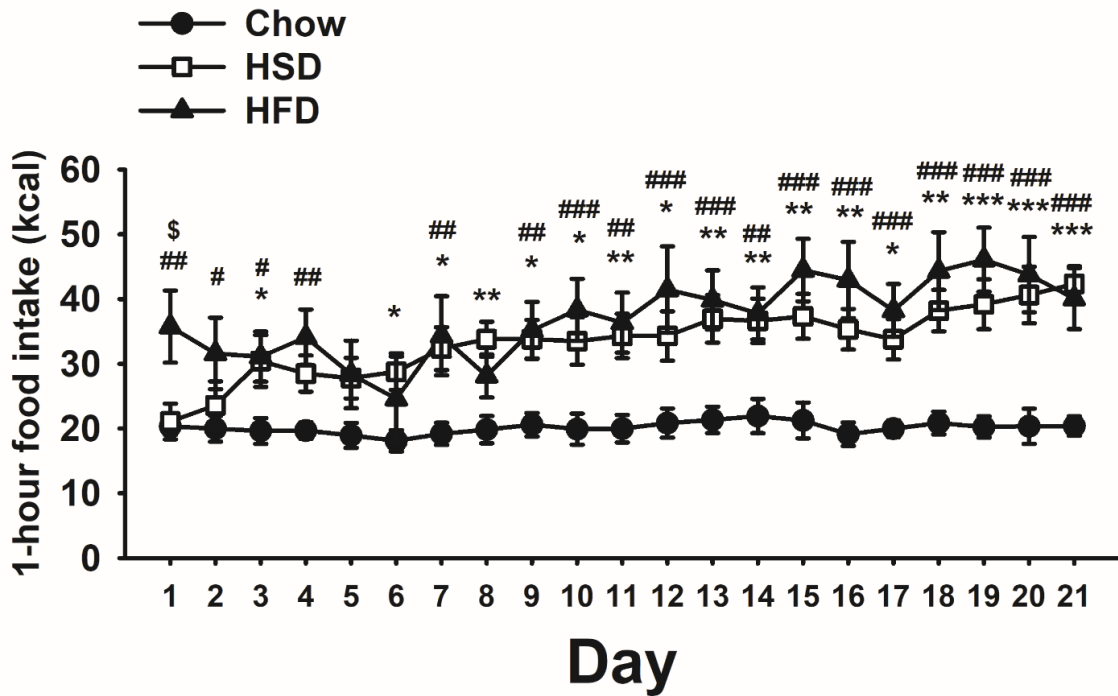


Figure 3. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on food intake (kcal) in female Sprague Dawley rats ($n=10/\text{group}$). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M \pm \text{SEM}$. Symbols denote: * HSD differs from Chow, $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; # HFD differs from Chow, $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$; \$ HSD differs from HFD, $p < 0.05$ (Fisher's Least Significant Difference (LSD) test).

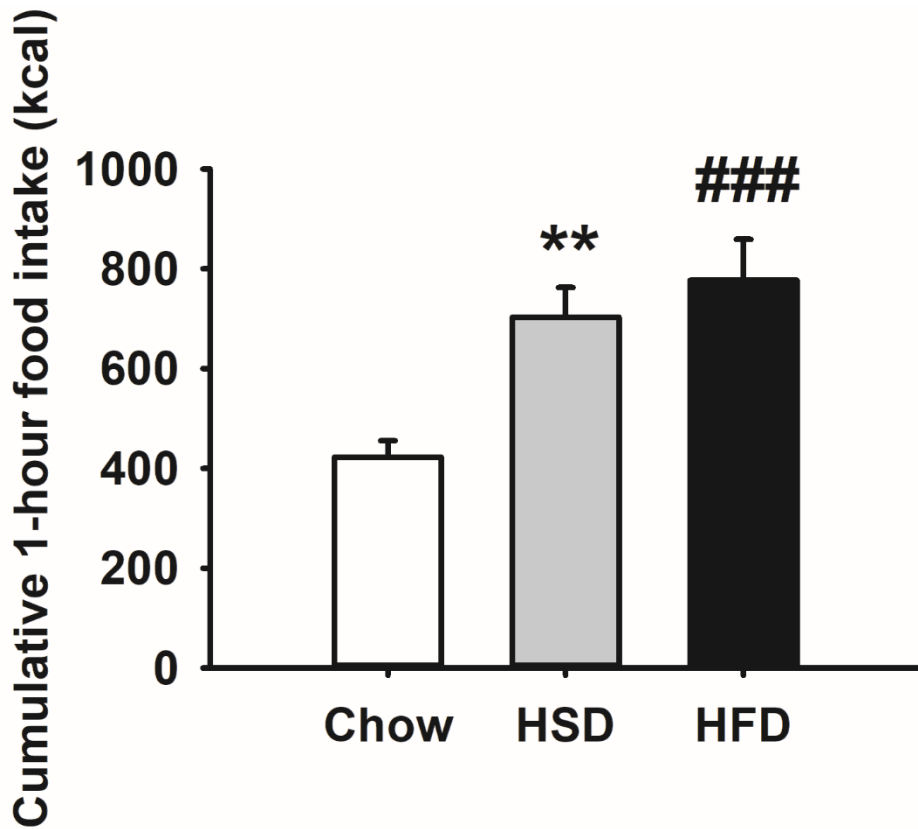


Figure 4. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on cumulative 1-hour food intake (kcal) in female Sprague Dawley rats ($n=10/\text{group}$). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M\pm\text{SEM}$. Symbols denote: ** HSD differs from Chow, $p<0.01$; ### HFD differs from Chow, $p<0.001$ (Fisher's Least Significant Difference (LSD) test).

Inter Food Intervals (IFI) (Ln(sec)). As shown in **Figure 5**, the statistical analysis of the ln-transformed duration of consecutive (uninterrupted by drinking) Inter Food Intervals (IFI) revealed a significant main effect of DIET (Diet: $F(2,27)=8.67, p<0.01$) a significant main effect of DAY (Day: $F(20,540)=12.42, p<0.001$) and a significant interaction DIET*DAY (Diet X Day: $F(40,540)=1.66, p<0.01$).

Chow control rats showed steady IFIs across the 21 days of observation. HSD rats showed a reliable decrease in IFIs as compared to Chow control starting from Day 1 and throughout the entirety of the study. Conversely, HFD rats showed a trend towards increase as compared to Chow rats during the first week of operant self-administration to then stabilize to a control level.

Therefore, only the high sugary diet was able to reliably increase the rate of intake as compared to controls, while the high fat diet did not.

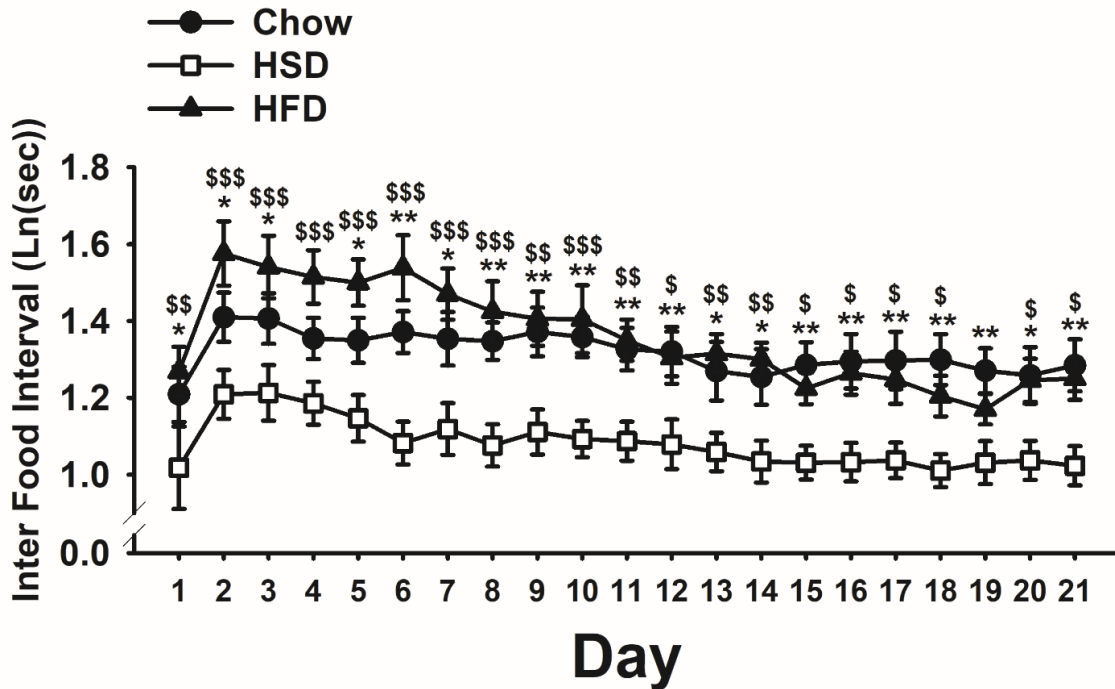


Figure 5. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on Inter Food Interval (IFI) (Ln(sec)) in female Sprague Dawley rats ($n=10$ /group). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M \pm SEM$. Symbols denote: * HSD differs from Chow, $p < 0.05$, ** $p < 0.01$; \$ HSD differs from HFD, $p < 0.05$, \$\$ $p < 0.01$, \$\$\$ $p < 0.001$ (Fisher's Least Significant Difference (LSD) test).

Effects of 1-hour Limited Access to Diets with Different Macronutrient Composition on Home-cage Food Intake, Daily Food Intake, and Cumulative Food Intake.

23-hour home-cage food intake (kcal). As shown in **Figure 6**, the statistical analysis of the 23-hour home-cage food intake revealed a significant main effect of DIET (Diet: $F(2,27)=4.50$, $p<0.05$) a significant main effect of DAY (Day: $F(20,540)=6.22$, $p<0.001$) and a significant interaction DIET*DAY (Diet X Day: $F(40,540)=2.98$, $p<0.001$).

Chow rats showed a steady home-cage intake throughout the study. HFD rats did not reliably show any difference as compared to control Chow rats. Conversely, HSD rats showed a progressive and slow decrease in the home cage food intake as compared to both Chow and HFD rats.

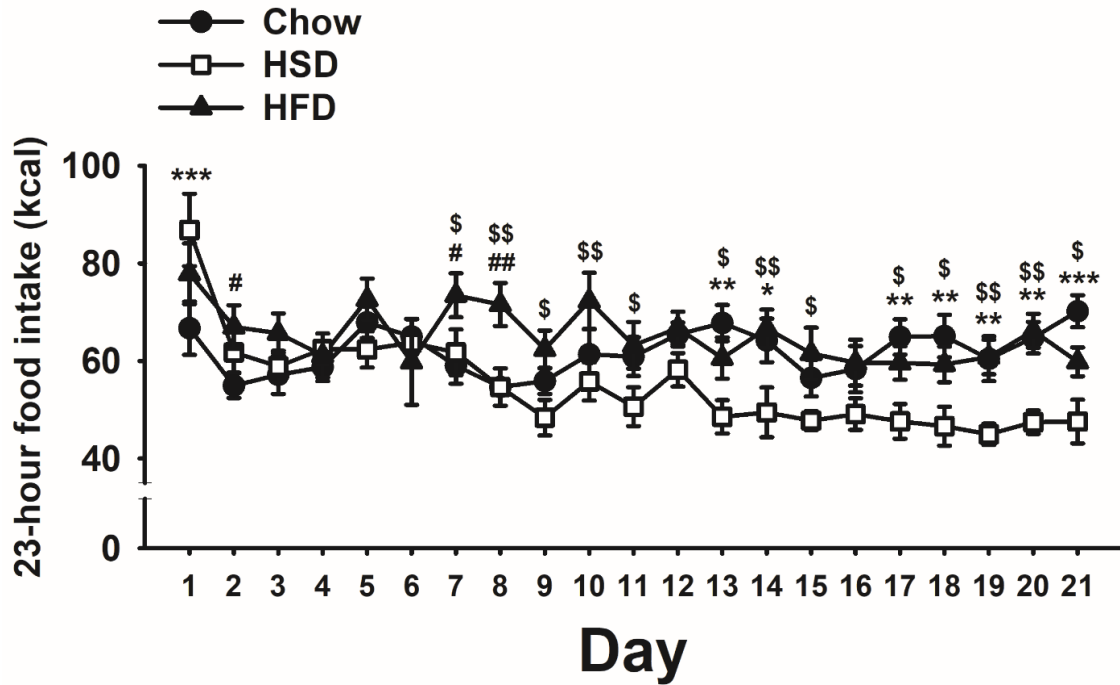


Figure 6. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on home-cage food intake (kcal) in female Sprague Dawley rats ($n=10/\text{group}$). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M \pm \text{SEM}$. Symbols denote: * HSD differs from Chow, $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; # HFD differs from Chow, $p < 0.05$, ## $p < 0.01$; \$ HSD differs from HFD, $p < 0.05$, \$\$ $p < 0.01$ (Fisher's Least Significant Difference (LSD) test).

24-hour daily food intake (kcal). As shown in **Figure 7**, the statistical analysis of the 24-hour daily food intake revealed a significant main effect of DIET (Diet: $F(2,27)=11.30, p<0.001$) a significant main effect of DAY (Day: $F(20,540)=2.81, p<0.001$) and a significant interaction DIET*DAY (Diet X Day: $F(40,540)=1.42, p<0.05$).

Chow rats showed a steady daily intake throughout the 21-day observation period. HSD rats, which consumed more energy than controls during the 1-hour operant self-administration session and decreased their food intake in the home cage, did therefore not reliably differ from Chow control rats on most days. Conversely, HFD rats, which consumed more energy than controls during the 1-hour operant self-administration session but did not decrease their home-cage food intake, showed a reliable increase in the 24-hour food intake as compared to Chow control rats as compared to HSD rats on most days.

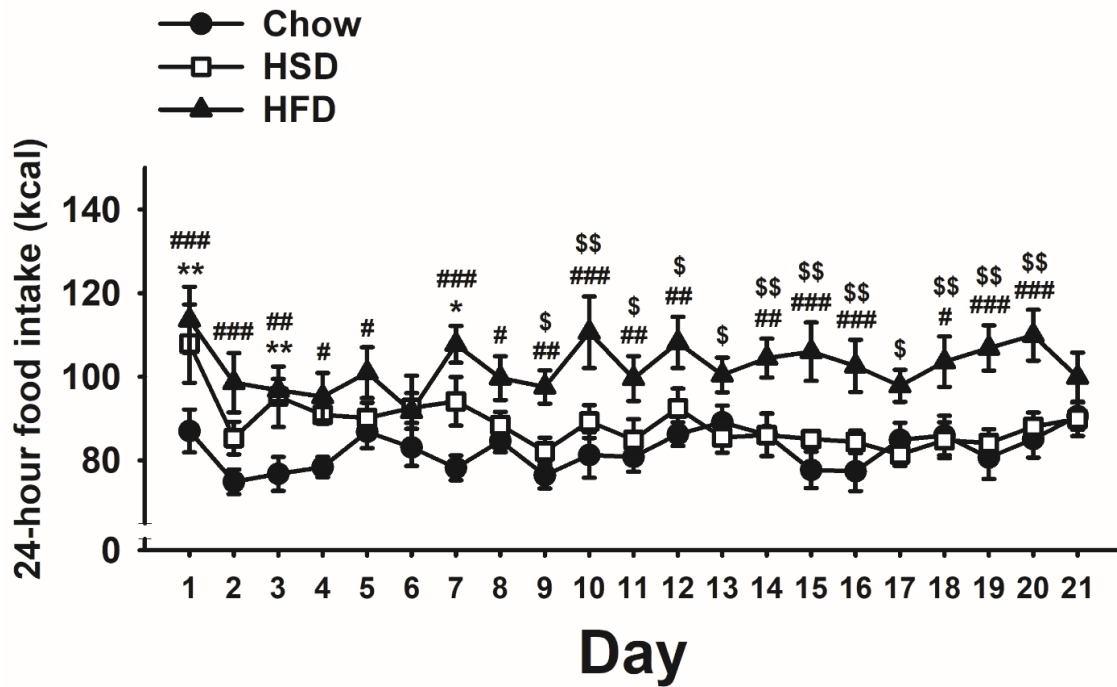


Figure 7. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on daily food intake (kcal) in female Sprague Dawley rats ($n=10/\text{group}$). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M \pm \text{SEM}$. Symbols denote: * HSD differs from Chow, $p < 0.05$, ** $p < 0.01$; # HFD differs from Chow, $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$; \$ HSD differs from HFD, $p < 0.05$, \$\$ $p < 0.01$ (Fisher's Least Significant Difference (LSD) test).

Cumulative food intake (kcal). As shown in **Figure 8**, the statistical analysis of the cumulative food intake revealed a significant main effect of DIET (Diet: $F(2,27)=11.46, p<0.001$) a significant main effect of DAY (Day: $F(20,540)=2442.21, p<0.001$) and a significant interaction DIET*DAY (Diet X Day: $F(40,540)=10.81, p<0.001$).

The pattern of intake of HFD rats in the 1-hour operant sessions and in the home-cage was such that made this group consume cumulatively more energy than any other group throughout the study.

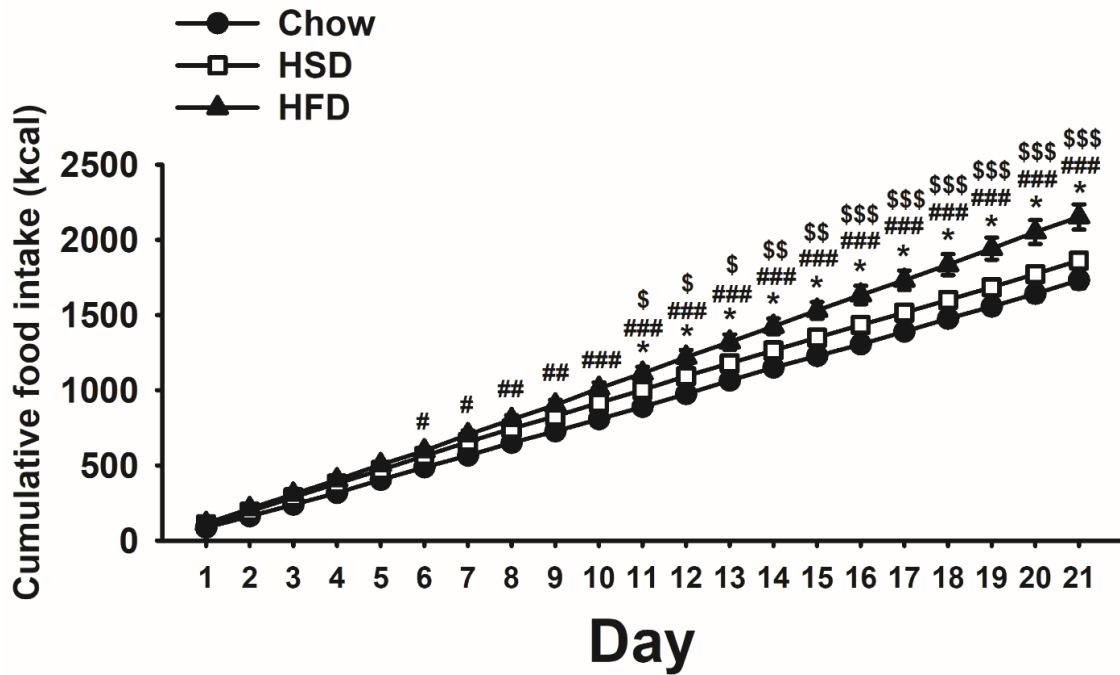


Figure 8. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on cumulative food intake (g) in female Sprague Dawley rats ($n=10$ /group). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M \pm SEM$. Symbols denote: * HSD differs from Chow, $p < 0.05$; # HFD differs from Chow, $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$; \$ HSD differs from HFD, $p < 0.05$, \$\$ $p < 0.01$, \$\$\$ $p < 0.001$ (Fisher's Least Significant Difference (LSD) test).

Effects of 1-hour Limited Access to Diets with Different Macronutrient Composition on Body Weight and Feed Efficiency.

Cumulative body weight gain (g). As shown in **Figure 9**, the statistical analysis of the cumulative body weight gain revealed a significant main effect of DIET (Diet: $F(2,27)=5.12, p<0.05$) a significant main effect of DAY (Day: $F(20,540)=210.84, p<0.001$) and a significant interaction DIET*DAY (Diet X Day: $F(40,540)=2.93, p<0.001$).

HSD rats showed a reliable increase in body weight gain as compared to the other groups throughout the study. Despite eating more calories than Chow rats, HFD rats instead did not reliably show any difference in body weight gain than controls.

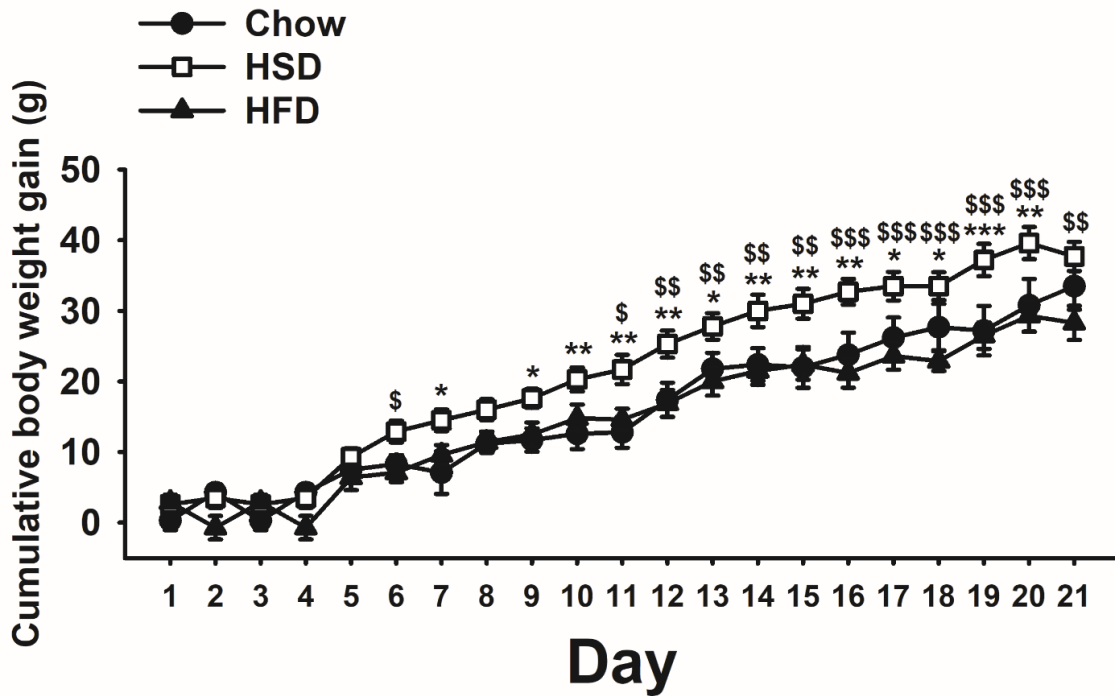


Figure 9. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on body weight gain (g) in female Sprague Dawley rats ($n=10/\text{group}$). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M \pm \text{SEM}$. Symbols denote: * HSD differs from Chow, $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; \$ HSD differs from HFD, $p < 0.05$, \$\$ $p < 0.01$ \$\$\$ $p < 0.001$ (Fisher's Least Significant Difference (LSD) test).

Cumulative feed efficiency (mg/kcal). As shown in **Figure 10**, the statistical analysis of the cumulative body weight gain revealed a significant main effect of DIET (Diet: $F(2,27)=4.17$, $p<0.05$) a significant main effect of DAY (Day: $F(20,540)=3.21$, $p<0.001$) and a significant interaction DIET*DAY (Diet X Day: $F(40,540)=1.89$, $p<0.01$).

Although main effect and interaction in the ANOVA were significant, very few effects were detected in the post-hoc analyses. The overall effects in the ANOVA were likely due to the higher feed efficiency of HSD throughout the study as compared to any other experimental group. This result was expected given that HSD group showed higher cumulative body weight gain than any other group but an unchanged cumulative food intake as compared to controls. Conversely, HSD rats, which gained as much weight as Chow rats but consumed less calories than controls, showed the smallest feed efficiency than any other group. Therefore, HSD rats consumed less kcal but gained more weight than HFD rats.

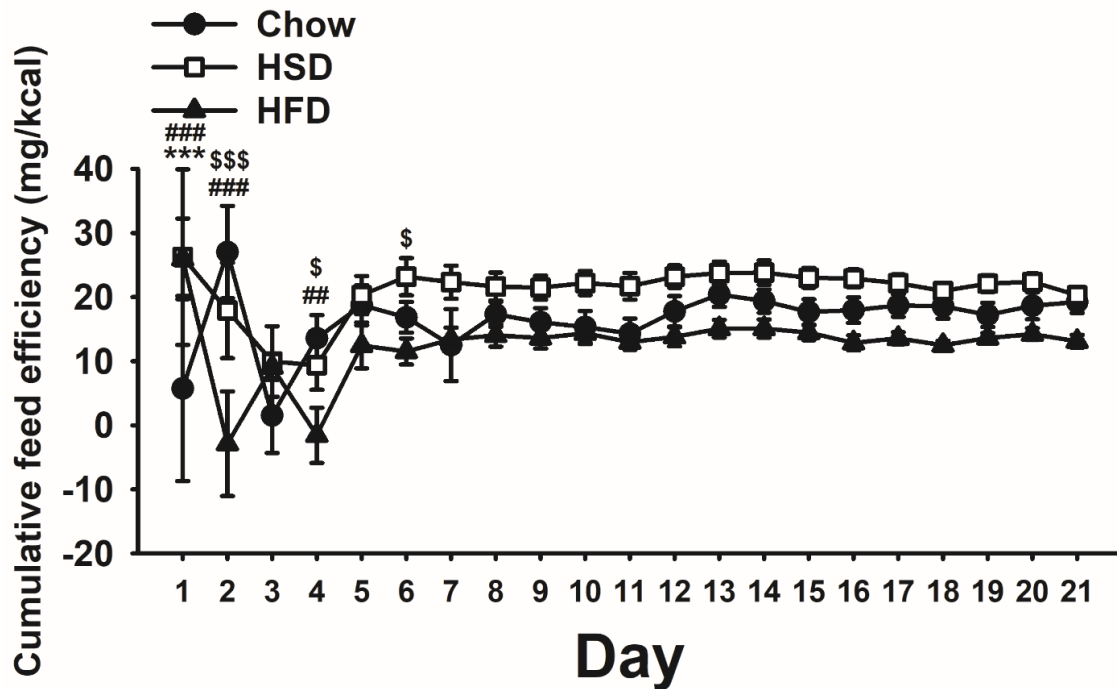


Figure 10. Effects of daily 1-hour self-administration of Chow, HSD, or HFD on cumulative feed efficiency (mg/kcal) in female Sprague Dawley rats ($n=10/\text{group}$). Rats were given the opportunity to self-administer one of the three diets in a Fixed Ratio 1 schedule during a 21-day period. Chow was otherwise freely available in the home cages. Panels represent $M \pm \text{SEM}$. Symbols denote: *** HSD differs from Chow, $p < 0.001$; ## HFD differs from Chow, $p < 0.01$ ### $p < 0.001$; \$ HSD differs from HFD, $p < 0.05$, \$\$\$ $p < 0.001$ (Fisher's Least Significant Difference (LSD) test).

DISCUSSION

In this study we show that limiting access to either a high-sucrose or a high-fat diet induces binge-like eating. However, we found that the nature of the two binge-like eating behaviors is substantially dissimilar, and differences can be summarized as follows: 1) binge-like eating of high-sucrose diet is based on an “active” increase of the amount food ingested, while binge-like eating of high-fat diet is based on “passive” energy consumption, due to the high energy density of the diet; 2) binge-like eating of the high-sucrose diet is accompanied by an increased eating rate, while limiting access to the high fat diet does not increase the eating rate; 3) rats bingeing on the high-sucrose diet decrease the home-cage intake of the standard chow diet, while rats bingeing on the high fat diet keep on consuming the same amount of standard chow returning to their home-cages; 4) since the rats bingeing on the high-fat diet do not undereat standard chow in the home cage, they end up consuming cumulatively more energy than the rats bingeing on the high-sucrose diet; 5) rats bingeing on the sucrose diet consume less energy, but gain more body weight and are therefore more energy-efficient than rats bingeing on the high-fat diet.

Binge-like eating behavior development

In this study we show that, when female rats are given the opportunity to self-administer either a high-sucrose or a high-fat diet, in either case they consume more energy than controls as typically observed in animal models of binge-like eating. 1-hour

food intake of both HSD and the HFD groups increased in magnitude nearly 2-fold compared to that of Chow control rats. Binge episodes were important as both HSD and HFD rats consumed between the 35% and the 40% of their daily intake in only 1-hour.

Therefore, the binge-like eating modeled in both HSD and HFD was isomorphic, as it was able to resemble the human symptomology. Indeed, certain criteria observed in human binge eating disorder were fulfilled: 1) both HSD and HFD female rats consumed in a discrete period (1-hour) an amount of food which is generally not eaten under similar circumstances in normal conditions (Chow control group). Additionally, the binge-like eating of female rats occurred repeatedly over an extended period of time. Finally, binge-like eating occurred in absence of hunger as rats were never food restricted/deprived (American Psychiatric Association, 2013).

However, binge-like eating in the two experimental groups was substantially different. As previously shown, while the excessive energy intake of the high-sucrose diet develops slowly as a function of the days of limited access (Blasio, Steardo, et al., 2014; Cottone et al., 2012; Ferragud et al., 2017; Moore et al., 2018; Smith et al., 2015a; Velazquez-Sanchez et al., 2014; Velazquez-Sanchez et al., 2015), rats with limited exposure to the high-fat diet consumed more calories than controls since the very first day of access. A more detailed analysis of feeding behavior in the operant chambers showed that the nature of the excessive intake of food in the two experimental groups was substantially different. Indeed, binge-like eating of the high-sucrose diet was due to a

true increase in the amount of food ingested, while the binge-like eating of the high-fat diet was due exclusively to the higher energy density of the food. In other words, HFD rats consumed the same amount of food than controls but, since it was more energy-dense than the standard chow diet, they ended up consuming more energy since the first day of access without any reliable escalation throughout the period of access. Therefore, we can say that rats exposed to the high-sucrose diet showed an “active” binge eating, which develops as function of the number of exposures, while rats exposed to the high-fat diet showed a “passive” binge eating which does not substantially change across days of access.

Interestingly, rats bingeing on the high-sucrose or the high-fat diet showed differences in how quickly the food was eaten. As observed in many papers previously published by our laboratory (Blasio, Steardo, et al., 2014; Cottone et al., 2012; Ferragud et al., 2017; Moore et al., 2018; Smith et al., 2015a; Velazquez-Sanchez et al., 2014; Velazquez-Sanchez et al., 2015), binge-like eating of the high-sucrose diet is accompanied by a dramatic decrease in the inter food interval (i.e. increase in eating rate). Similar to the increased sucrose licking rate, this effect has been interpreted as dependent on the higher palatability of the diet as compared to the standard chow food (Wassum, Ostlund, Maidment, & Balleine, 2009). Conversely, the passive binge-like eating of the high-fat diet occurred at the same eating rate as controls. Therefore, we can confidently say that the high-fat diet was not more palatable than the standard control

diet, and this may be the reason of why the amount of food ingested was not different than controls.

This interpretation is also supported by another finding, which further emphasizes the differences between the two behavioral outcomes: while the rats exposed to the high-sucrose diet in the operant conditioning boxes decreased the intake of the standard chow diet when returning into the home-cages, rats exposed to the high-fat diet instead did not and kept on eating as much as controls. This finding is particularly relevant, because it may also help clarify the nature of the hypophagia of a less preferred food alternative in more general terms. Undereating of less preferred food (e.g., chow hypophagia) has been traditionally explained as a corrective energy-homeostatic response to the recent excess energy intake (Archer et al., 2005; Corwin, 2004). However, other explanations have been provided to explain this phenomenon which do not involve energy-homeostatic mechanisms, but instead relate to non-nutritional and hedonic component of feeding. These alternative interpretations include “negative contrast” (Cottone, Sabino, Roberto, et al., 2009; Cottone et al., 2008b; Cottone, Sabino, Steardo, et al., 2009), due to recent exposure to or the upcoming access to a more rewarding alternative (Flaherty, Coppotelli, Grigson, Mitchell, & Flaherty, 1995; Grigson, Spector, & Norgren, 1993), “palatable food withdrawal,” similar to the negative emotional state observed with drugs of abuse (Blasio et al., 2013; Cottone, Sabino, Roberto, et al., 2009), and opponent-process shifts in brain reward function (Solomon & Corbit, 1974). Our findings support the notion of a non-nutritional, but rather a hedonic mechanism underlying the hypophagia of the less

preferred chow diet in the home-cage. Indeed, if the hypophagia was simply due to a corrective energy-homeostatic response to the previous caloric load, since the high-fat diet exposed rats did eat more calories than controls since day 1 of access, then we should have observed the hypophagia of the standard chow diet in the home-cage in that group as well; however, this was not the case. Instead, only rats exposed to the high-sucrose diet (but not the ones exposed to the high-fat diet) which showed an “active” increase in the amount of food eaten and an increased eating rate due to the palatability of the diet, showed the hypophagia of the standard chow diet in the home-cage. Therefore, we can reasonably conclude that the high-fat diet was not more palatable than the standard chow diet, as instead was the case for the high-sucrose diet, and that for this reason female rats exposed to the HFD did not ingest a bigger amount of food than controls in the operant conditioning boxes, did not eat faster than controls, and did not reject the home cage standard chow as high-sucrose diet rats did.

It is important to note that not all the high-fat diets may generate the same behavioral outcomes observed in this study. Indeed, it has been shown that oils with different fat composition can be differently palatable as measured by licking rate (Yoneda et al., 2009). So we cannot exclude that using diets with different fat composition may produce different outcomes than the ones observed here.

Cumulative intake, body weight gain and feed efficiency

In this study we observed that the rats exposed to the high-fat diet consumed more energy than both control and HSD rats. This outcome resulted from both the passive intake in the 1-hour self-administration procedure and the inability to reduce the intake in the home cage. Surprisingly, rats exposed to the high-fat diet, despite consuming more energy than any other group, did not gain more weight than controls. Instead, rats exposed to the high-sucrose diet, which consumed less energy than HFD were the heaviest. Therefore, HSD rats consumed less calories but gained more weight than HFD rats, resulting in a more energy-efficient phenotype.

Conclusions

In this study we show that limiting access to either a high-sucrose or a high-fat diet can produce very different outcomes. Although both of the diets, when provided for only 1-hour/day, can promote binge-like eating, the nature of the two excessive behaviors is substantially different: binge-like eating of high-sucrose diet is based on a true increase in the amount of food consumed, in an increased eating rate, which suggests an increased palatability, and a decrease in the home-cage standard chow intake, likely due to a negative contrast effect. Conversely, binge-like eating of the high-fat diet is a result of passive energy consumption and the high energy-density of the food. Additionally, HFD binge-like eating is accompanied by neither increased eating rate nor rejection of the standard chow diet in the home-cages. Moreover, while high-sucrose diet bingeing rats consume less energy than high-fat diet bingeing rats, the former are more energy efficient

and gain more body weight than the latter.

These results provide information on how the quality of food can deeply influence the behavioral and metabolic outcomes of binge-like eating.

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