Published in final edited form as:

Physiol Behav. 2015 May 1; 143: 136–141. doi:10.1016/j.physbeh.2015.03.002.

CORN OIL, BUT NOT COCAINE, IS A MORE EFFECTIVE REINFORCER IN OBESE THAN IN LEAN ZUCKER RATS

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Abstract

Obesity is associated with abnormal brain reactivity in response to palatable food consumption, a factor that may contribute to non-homeostatic eating. However, little is known about how obesity interacts with the reinforcing effects of highly palatable constituents of food (e.g., fat), and if altered reinforcement processes associated with obesity generalize to non-food reinforcers. The current study compared the reinforcing effects of a fat (corn oil) and a drug of abuse (cocaine) in obese and lean Zucker rats. Specifically, obese and lean Zucker rats self-administered corn oil or intravenous cocaine in a behavioral economic demand procedure. For corn oil, maximum demand was higher and demand elasticity was lower in the obese rats compared to their lean counterparts. However, there were no differences in demand for cocaine between the obese and lean rats. These results demonstrate that a fat in the form of corn oil is a more effective reinforcer in obese Zucker rats. However, the fact that demand for cocaine was not different between the obese and lean rats suggests that differences in reward mechanisms may be reinforcer-specific and do not necessarily generalize to non-food reinforcers.

Keywords

Obesity; reinforcement; Zucker rat; fat; cocaine; behavioral economics

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1 Introduction

Rates of obesity in the United States have increased 40-50% in the past twenty years (Leonard, 2014). Over the same time period, measures of physical activity have decreased and caloric intake has risen, indicating an increase in non-homeostatic eating (Leonard, 2014). Consuming excessive amounts of energy-dense, highly palatable foods contributes to obesity onset and maintenance (Frascella et al., 2010). It has been suggested that highly palatable foods may be more reinforcing in obese than in lean individuals, thus enhancing vulnerability for over-eating (see Volkow et al., 2013 for review). Obese humans rate high-fat and high-sugar foods as more pleasant and also prefer palatable food mixtures with a higher ratio of fat than do non-obese subjects (Drewnowski et al., 1985; Rissanen et al., 2002). Furthermore, obese subjects have altered brain activation in response to palatable food anticipation and consumption (Gearhardt et al., 2011). However, little is known about how obesity interacts with the reinforcing effects of specific macronutrients like fat and sugar.

A number of animal models have been used to study the effects of obesity on food reinforcement (Castonguay et al., 1982; Colby and Smith, 1975; Finger et al., 2010; Marco et al., 2012; Wellman et al., 2007). One model is the genetically obese Zucker rat. Obesity in the Zucker rat is thought to be due to a recessive mutation of the leptin receptor that renders leptin signaling relatively weak, thus resulting in hyperphagia and excessive weight gain (Phillips et al., 1996). Similar to human imaging studies, obese Zucker rats exhibit altered neural responses to food stimuli, suggesting that food reinforcement may differ in obese versus lean Zucker rats (Thanos et al., 2008a). This model of obesity has also been applied to multiple parameters of food reinforcement. In measures of food self-administration, obese Zucker rats earn more grain pellets than leans on a fixed-ratio (FR) schedule of reinforcement (Glass et al., 1999). Furthermore, obese Zucker rats achieve higher breakpoints on a progressive-ratio (PR) schedule of reinforcement for grain pellets than their lean counterparts (Glass et al., 1999). Notably, group differences in food-pellet self-administration disappear when Zucker rats are food-restricted (Thanos et al., 2008b), suggesting that the relative effects of food restriction on food reinforcement differ between obese and lean Zucker rats.

Sugar and fat are highly palatable macronutrients that are often present in energy-dense food. By studying the reinforcing effects of sugar and fat under discrete conditions, a more precise assessment of the relative contributions of these macronutrients on the reinforcing effects of food is possible. Available evidence indicates that the reinforcing effect of sucrose is comparable in obese and lean Zucker rats. For example, breakpoints for sucrose pellets under a PR schedule of reinforcement are similar between obese and lean Zucker rats (Rasmussen and Huskinson, 2008). Furthermore, demand elasticity for sucrose pellets in obese and lean Zucker rats is comparable (Rasmussen et al., 2010). However, evidence suggests that the reinforcing effects of fat may differ between obese and lean Zucker rats. For example, when given free access to discrete fat, carbohydrate, and protein sources, obese Zucker rats select a higher proportion of their calories from fat than do their lean counterparts (Castonguay et al., 1982). Furthermore, when Zucker rats are given a choice between sucrose and corn oil, a higher concentration of sucrose is required to draw

preference away from corn oil in the obese rats, suggesting that the relative reinforcing effects of corn oil and/or sugar are not the same in lean and obese Zucker rats (Greenberg and Weatherford, 1990).

Based on the higher preference for fat in the obese Zucker rat, we hypothesized that a fat would be a more effective reinforcer in obese rats than in their lean counterparts. To that end, the current study quantified the relative reinforcing effectiveness of corn oil in obese and lean Zucker rats using a behavioral economic approach (Hursh and Silberberg, 2008). The behavioral economic procedure we used is based on “demand curves,” where consumption is plotted as a function of price. The data are then fit with Hursh and Silberberg's (2008) Exponential Model of Demand, which defines a reinforcer's strength by quantifying its sensitivity to price (demand elasticity; see Hursh, 2014; Hursh and Roma, 2013; Hursh and Silberberg, 2008). An advantage of this approach is that the exponential model can compare the relative effectiveness of a reinforcer between groups even when intake differs at the lowest cost (or in the present case, FR1). Given that obese Zucker rats consume food at a higher rate than their lean counterparts under both *ad lib* and operant conditions (Castonguay et al., 1982; Glass et al., 1999; Rasmussen et al., 2010), a behavioral economic approach is well suited for the current research question.

Additionally, recent research suggests that obese individuals and drug abusers express common neuronal adaptations related to reward processing, which in turn mediates their overeating and drug abuse, respectively (DiLeone et al., 2012; Kenny, 2011; Volkow et al., 2011; Volkow et al., 2013). However, it is unknown if altered responsiveness to food reward related to obesity can generalize to a drug of abuse. Previous application of the behavioral economic approach identified differences in the reinforcing strength of drug and food reinforcers between rat strains (e.g., Christensen et al., 2009). Thus, the current study used a similar approach to determine the relative reinforcing effectiveness of cocaine in obese and lean Zucker rats.

2 Method

2.1 Subjects

Male Zucker rats (Harlan Laboratories, New Jersey, USA) were used in the experiments. Rats used in the corn oil demand experiment arrived at 4-5 weeks of age and were acclimated for three weeks before training began. Rats in the cocaine demand experiment arrived at 9-10 weeks of age and began training upon arrival. Rats were individually housed throughout the experiments. All housing and testing were conducted in a temperature-controlled vivarium (23°C) with a 12-h light/dark cycle with lights on at 0800 hours. All behavioral testing occurred in the light phase. Rats were given *ad libitum* access to standard chow and water throughout the study. All procedures were conducted in compliance with the National Research Council's Guide for Care and Use of Laboratory Animals (2011) and approved by the University of Mississippi Medical Center's Institutional Animal Care and Use Committee.

2.2 Apparatus

Eight custom operant chambers (Gerbrands Corporation; 19 cm h × 23.5 cm w × 22 cm l) equipped with two non-retractable levers (Gerbrands Corporation) capable of delivering reinforcers in the form of pellets, liquids, or intravenous drug infusions were used for all procedures. A single white stimulus light was mounted above each lever. Food pellets (45 mg; Bio-Serve, Frenchtown, New Jersey, USA) were delivered by a pellet dispenser (Gerbrands Corporation) into a food tray located between the levers. Corn oil was delivered from 30 ml glass syringes that were seated in infusion pumps (Razel Scientific, St. Albans, VT, USA) located outside the operant box. Corn oil deliveries traveled through polyethylene tubing and were deposited into a metal trough located below the lever. For cocaine self-administration, drug was delivered from 30 ml plastic syringes using the same pumps as above. The polyethylene pump tubing was connected to a swivel located above the operant chamber from which a spring-arm leash was suspended. The terminal end of the leash consisted of a needle and a threaded tether that connected to the septum of a vascular access port (Instech Laboratories, Plymouth Meeting, PA, USA) implanted into the midscapular area of the rat's back (see Surgery). Test sessions were conducted seven days per week. A Macintosh computer with custom interface and software (Mac State) controlled all events in the experimental session and recorded data.

2.3 Procedure

2.3.1 Food Training—All rats were trained in two-hour sessions to press the active (right) lever for food pellets. A stimulus light was illuminated above the active lever. Presses on the inactive (left) lever were recorded, but had no programmed consequences. During food training, rats were food-restricted to approximately 20g of chow (Harlan, Madison, WI, USA) per day to aid in acquisition of lever pressing. Initially, food-training sessions were conducted with the active lever baited with taped food pellets under a fixed-ratio 1 (FR 1) schedule of reinforcement. After 50 food pellets were earned in a single session without baiting, the FR was progressively increased over days to a terminal FR of 10. Operant response acquisition was defined as earning 50 food pellets in a single session under a FR 10 schedule of reinforcement.

2.3.2 Surgery—Rats used in the cocaine self-administration experiment were implanted with chronic intravenous catheters. Rats were anesthetized with isoflurane and the right jugular vein was isolated, punctured, and implanted with a polyethylene catheter (Instech Laboratories, Plymouth Meeting, PA, USA). Next, an incision was made approximately one centimeter posterior to the scapulae. The unsecured end of the catheter was then routed, subcutaneously, to the site of the incision and connected to the vascular access port. Rats were given five days to recover from surgery before starting the operant procedure. To prevent infection and maximize catheter patency, catheters were flushed daily with 0.1 ml of gentamicin (0.8 mg/ml) and 0.1 ml of heparinized saline (40 U/ml) before sessions, and 0.1 ml of heparinized saline (100 U/ml) after sessions. All catheters were periodically tested for patency by injecting 0.1 ml of ketamine (50 mg/ml) followed by 0.1 ml of heparinized saline (40 U/ml). Catheters were considered patent if ataxia was apparent within ten seconds of injection. If a catheter was considered non-functional, a new catheter was implanted into the left jugular vein according to the above protocol and the animal continued in the experiment.

One rat from the lean group was implanted with a left jugular catheter and subsequently restarted the demand procedure.

3.4 Experiment 1: Corn Oil Demand

Eight lean and eight obese Zucker rats self-administered corn oil (0.1 ml/ delivery) in daily one-hour sessions. Mazola® corn oil was used in all sessions (ACH Food Companies, Inc. Memphis, TN, USA). After an animal met the stability criterion for pellet self-administration, lever pressing for corn oil was placed under an FR1 schedule of reinforcement until responding was stable, defined as three consecutive days of reinforcer deliveries that were within 20% of the 3-session mean with no upward or downward trends. Subsequently, the FR was increased across sessions in the following order: 1, 3, 10, 18, 32, 56, 100, 180, and 320. Each FR condition was in effect until the stability criterion used at FR 1 was met. Fixed-ratio values were progressively increased until no reinforcers were earned for two consecutive sessions.

3.5 Experiment 2: Cocaine Demand

Five lean and five obese Zucker rats self-administered intravenous cocaine (0.75 mg/kg/inj) in daily one-hour sessions. The FR progression was the same as in Experiment 1. To mitigate the effects of catheter failure on the completion of the experiment, the stability criterion was loosened for Experiment 2. Specifically, rats self-administered cocaine under an FR 1 schedule of delivery until there were three consecutive sessions within 20% of the three-session mean with no trends, but subsequent FRs were increased every two or three days. After FR 1 was complete, the FRs were increased after two days if reinforcers earned in those days were within 20% of the two-session mean. Otherwise, a third day was added before progressing to the next FR. Thus, no more than three sessions were conducted at a single FR value.

3.6 Drugs

Cocaine hydrochloride was generously provided by the National Institute on Drug Abuse (Rockville, MD, USA). Solutions were prepared in 0.9% saline. All doses are expressed as the salt.

3.7 Data Analysis

Acquisition of stable corn oil or cocaine self-administration (i.e., stable FR1 consumption) was compared between lean and obese rats within a reinforcer condition (i.e., corn oil or cocaine) using unpaired *t*-tests. For each experiment, reinforcer value was determined using a behavioral economic demand curve approach (Hursh and Silberberg, 2008), which relates the consumption of a reinforcer (i.e., the number of reinforcers earned per session) to its price (i.e., the FR for one reinforcer delivery). A custom-designed GraphPad Prism 5.0 template (freely available from the Institutes for Behavior Resources, www.ibrinc.org) plotted reinforcers earned in a session as a function of FR value and the data were fit with the Exponential Model of Demand introduced by Hursh and Silberberg (2008). In cases where the injections per session were a value of 0 (i.e., responses were not sufficient to earn

a reinforcer), a value of 0.1 was entered because the log of 0 cannot be calculated (see Banks et al. 2011; Freeman et al., 2014).

For both the corn oil and cocaine demand curves, baseline consumption (i.e., consumption at FR1) and demand elasticity (α) were the dependent measures of interest with strain (i.e., obese vs. lean) as the independent variable. The α values were derived from the analyses of the aggregated mean demand curves generated with three stable sessions of corn oil self-administration or the last two sessions of cocaine self-administration per FR value. Hursh and colleagues (Hursh and Silberberg 2008; Hursh and Roma, 2013) have argued that reinforcing effectiveness or “Essential Value” has an inverse relationship to elasticity of demand (α ; i.e., sensitivity to price). With this in mind, demand elasticity was presented graphically as Essential Value such that a larger value reflects a greater reinforcing effectiveness. That formula was recently introduced by Hursh (2014) and is given in equation 1:

$$\text{Essential Value} = 1 / (100 \bullet \alpha \bullet k^{1.5})$$

Mann-Whitney *U* Tests were used to compare group medians for baseline intake (i.e., intake at FR 1) and Essential Value for corn oil and cocaine in obese and lean rats because variances were found to be unequal in some comparisons. Demand elasticity (α) of aggregated demand curves within each reinforcer type (corn oil or cocaine) were compared using the extra sum-of-squares *F* test. Statistical significance for all tests was set at $p = 0.05$. Unless otherwise noted, all data are presented as mean $\pm$ SEM.

4 Results

Rates of acquisition of stable corn oil or cocaine self-administration were not different in obese and lean rats, as evidenced by similar numbers of sessions required before stability criteria were met for both corn oil (obese: 14.50 ± 1.7 , lean: 14.75 ± 1.2 , $p = 0.49$) and cocaine (obese 5.6 ± 0.87 , lean: 6.6 ± 1.4 , $p = 0.52$). As the FR value increased over sessions, consumption of both corn oil and cocaine decreased. Figure 1, Panel A illustrates mean aggregated demand curves for corn oil in obese versus lean rats. The Exponential Model provided a good fit to the aggregated data (R^2 values were .98 for obese and .94 for lean rats). Demand for corn oil was less elastic in the obese than in the lean rats ($F(1,13) = 153$, $p < 0.001$). Panel B illustrates maximum demand for corn oil, i.e., consumption at the lowest FR (i.e., FR 1). Obese rats earned more corn oil deliveries than lean rats at FR 1 ($U = 7$, $p = 0.007$). Panel C illustrates the Essential Value for corn oil based on Exponential Model calculations. The Essential Value of corn oil was significantly larger (i.e., demand elasticity was smaller) for obese rats than their lean counterparts ($U = 5$, $p = 0.003$), indicating that corn oil was a more effective reinforcer in the obese rats.

Figure 2, Panel A illustrates mean aggregated demand curves for 0.75 mg/kg/inj of cocaine in obese and lean rats. Again, the Exponential Model provided a good fit to the aggregated data (R^2 values were .99 for obese and .89 for lean rats). Demand elasticity for cocaine was not significantly different between the obese and lean rats ($F(1,9) = 0.19$, $p > 0.60$). Panel B

illustrates maximum demand for cocaine. Obese and lean rats did not differ in cocaine intake at the lowest FR value ($U = 11.5$, $p = 0.88$). Panel C illustrates Essential Value for cocaine. No significant differences were observed in Essential Value of cocaine in obese versus lean rats ($U = 10$, $p = 0.67$). In summary, cocaine reinforcement was similar between lean and obese Zucker rats.

5 Discussion

The main finding of the present study was that the reinforcing effectiveness of corn oil, a fat, was greater in obese Zucker rats than in their lean counterparts. However, this difference did not generalize to cocaine, a non-food reinforcer. These results are consistent with previous findings suggesting that obese Zucker rats allocate more behavior to the consumption of fat than do their lean counterparts (Catanguay et al., 1982; Greenberg & Weatherford, 1990; Thanos et al., 2013). Previous reports demonstrating that the reinforcing effects of sucrose are similar in lean and obese Zucker rats (Glass et al., 1999; Rasmussen and Huskinson, 2008; Rasmussen et al., 2010; Rasmussen et al., 2012), when taken together with our demonstration of equivalent reinforcing effectiveness of cocaine in these animals, suggest that obesity may be specifically maintained by a heightened reinforcing effect of fat. However, comparison of the reinforcing effectiveness of other macronutrients (e.g., carbohydrate, protein) should be made before making firm conclusions on this issue.

The reinforcing properties of fat have been the focus of a growing body of research (see DiPatrizio, 2014 for a recent review). As stated previously, preference for fat versus other macronutrients has been observed in obese humans as well as obese Zucker rats when compared to non-obese controls (Catanguay et al., 1982; Drewnowski et al., 1985; Greenberg & Weatherford, 1990; Rissanen et al., 2002). Furthermore, imaging studies have reported that obese humans exhibit abnormal brain responsiveness to the taste of fatty foods compared to non-obese subjects (Gearhardt et al., 2011; Stice et al., 2009). Like obese humans, both obese Zucker rats and outbred rats made obese on experimental “cafeteria diets” exhibit decreased dopamine D2 receptor expression within the ventral striatum (Johnson and Kenny, 2010; Thanos et al., 2008a; Tomasi and Volkow, 2013). Similar findings have also been reported in rats self-administering cocaine over repeated, relatively lengthy daily sessions (Ahmed et al., 2002). Thus, as has been proposed for outbred rats given chronic cafeteria diet or drugs of abuse (Johnson and Kenny, 2010; Wang et al., 2002), a hyposensitive dopamine system may be responsible for the increased reinforcing effectiveness of corn oil in the Obese Zucker rat. However, altered D2 expression is not likely a complete account for differences in fat reinforcement in obese and lean Zucker rats because these changes would also be expected to affect cocaine reinforcement, which we did not observe.

To our knowledge, the current study is the first published investigation of drug reinforcement in genetically obese rats. Overall, relations between obesity and drug reinforcement are highly understudied and poorly understood. In a previous study, Wellman et al. (2007) reported that acquisition of cocaine self-administration was reduced in rats given a 45-day exposure to a high-fat diet. Importantly, this dietary manipulation produced the effect independent of obesity. These results, coupled with the results of the current study,

suggest that drug reinforcement can be altered by diet history but not necessarily by obesity in rats. Much discussion has occurred in recent years regarding the behavioral and neuronal commonalities associated with obesity and drug abuse, particularly in areas that govern reinforcement (DiLeone et al., 2012; Kenny, 2011; Volkow et al., 2011; Volkow et al., 2013). Given this overlap, a logical question is do conditions (such as obesity) that enhance behavioral and neuronal responsiveness to food reinforcement generalize to drug reinforcers, and vice versa? The current results suggest not. This is an interesting finding because, as stated above, obese Zucker rats express many of the neuronal adaptations that have been shown to occur in outbred rats and humans given chronic exposure to high-calorie foods and drugs of abuse (Gearhardt et al., 2011; Johnson and Kenny, 2010; Liang et al., 2006; Thanos et al., 2008a). It should be noted, however, that there are several dimensions of drug reinforcement that our behavioral economic approach is not equipped to measure (e.g., reinforcing potency, strength of drug-cue associations). These parameters should be tested before firm conclusions on the commonalities and differences in drug reinforcement are drawn in these strains.

When interpreting results from the current study, it is important to consider both the similarities and differences of obese Zucker rats and obesity in humans. Obesity in humans is almost exclusively diet-induced (McKenney and Short, 2011). Conversely, obesity in the Zucker rat arises from a genetic mutation that renders the animals relatively insensitive to the satiety hormone leptin, and thus leads to overeating (Fulton et al., 2004). Although some obese humans have congenital leptin deficiencies, the incidence is rare (Farooqi & O'Rahilly, 2005). Thus, generalizations between human obesity and genetic obesity in a rat model should be made with caution. However, humans do develop leptin resistance as a function of overeating, which may perpetuate overeating and obesity in a manner similar to the Zucker obese rat (Scarpace & Zhang, 2009). A logical next step will be to use the current design to test the reinforcing effects of palatable macronutrients (e.g., fat and sugar) and drugs of abuse in obese and lean outbred rats to determine if the current findings generalize to a diet-induced model of obesity.

In summary, the current data demonstrate that corn oil is a more effective reinforcer in obese Zucker rats than in their lean counterparts. If fats are particularly strong reinforcers in obese humans, too, then intervention strategies such as imposing taxes or any other additional cost requirements to acquiring fat-rich foods may be less effective for obese compared to non-obese people. However, if a treatment lowers the reinforcing effectiveness of fatty foods, increases in price could be more effective at decreasing non-homeostatic eating patterns in obese people. As such, identifying interventions that decrease the reinforcing effectiveness of fat in the obese Zucker rat could prove useful for better understanding the behavioral and biological dynamics underlying obesity in humans.

Acknowledgements

The current study was funded by grant R03DA031835 to K.B.F and the Intramural Research Support Program at the University of Mississippi Medical Center. The authors gratefully acknowledge the expert technical assistance of Steven Ross and Jacob Smith.

References

- Ahmed SH, Kenny PJ, Koob GF, Markou A. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. *Nat. Neurosci.* 2002; 5:625–626. [PubMed: 12055635]
- Banks ML, Roma PG, Folk JE, Rice KC, Negus SS. Effects of the delta-opioid agonist SNC80 on the abuse liability of methadone in rhesus monkeys: a behavioral economic analysis. *Psychopharmacology.* 2011; 216(3):431–9. [PubMed: 21369752]
- Buckley JL, Rasmussen EB. Rimonabant's reductive effects on high densities of food reinforcement, but not palatability, in lean and obese Zucker rats. *Psychopharmacology.* 2014; 231(10):2159–70. [PubMed: 24398820]
- Castonguay TW, Hartman WJ, Fitzpatrick EA, Stern JS. Dietary self-selection and the Zucker rat. *J Nutr.* 1982; 112(4):796–800. [PubMed: 7069514]
- Christensen CJ, Kohut SJ, Handler S, Silberberg A, Riley AL. Demand for food and cocaine in Fischer and Lewis rats. *Behavioral Neuroscience.* 2009; 123(1):165–171. [PubMed: 19170441]
- Colby JJ, Smith NE. Ability of rats with ventromedial hypothalamic lesions to work: Effects of ambient temperature. *Physiology and Behavior.* 1975; 15(1):31–5. [PubMed: 1197396]
- DiLeone RJ, Taylor JR, Picciotto MR. The drive to eat: comparisons and distinctions between mechanisms of food reward and drug addiction. *Nat Neurosci.* 2012; 15:1330–5. [PubMed: 23007187]
- DiPatrizaro NV. Is fat taste ready for prime time?. *Physiol Behav.* 2014; S0031-9384(14):00136–X.
- Drewnowski A, Brunzell JD, Sande K, Iverius PH, Greenwood MR. Sweet tooth reconsidered: taste responsiveness in human obesity. *Physiol Behav.* 1985; 35(4):617–22. [PubMed: 4070436]
- Farooqi IS, O'Rahilly S. 20 years of leptin: human disorders of leptin action. *J Endocrinol.* 2014; 223(1):T63–7D. [PubMed: 25232148]
- Finger BC, Dinan TG, Cryan JF. Progressive ratio responding in an obese mouse model: Effects of fenfluramine. *Neuropharmacology.* 2010; 59(7-8):619–626. [PubMed: 20727362]
- Frascella J, Potenza MN, Brown LL, Childress AR. Carving addiction at a new joint? Shared brain vulnerabilities open the way for non-substance addictions. *Ann N Y Acad Sci.* 2010; 1187:294–315. [PubMed: 20201859]
- Freeman KB, McMaster BC, Roma PG, Woolverton WL. Assessment of the effects of contingent histamine injections on the reinforcing effectiveness of cocaine using behavioral economic and progressive-ratio designs. *Psychopharmacology.* 2014; 231(12):2395–403. [PubMed: 24398822]
- Fulton S, Richard D, Woodside B, Shizgal P. Food restriction and leptin impact brain reward circuitry in lean and obese Zucker rats. *Behav Brain Res.* 2004; 155(2):319–29. [PubMed: 15364492]
- Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Arch Gen Psychiatry.* 2011; 68(8):808–16. [PubMed: 21464344]
- Glass MJ, O'Hare E, Cleary JP, Billington CJ, Levine AS. The effect of naloxone on food-motivated behavior in the obese Zucker rat. *Psychopharmacology.* 1999; 141(4):378–84. [PubMed: 10090645]
- Greenberg D, Weatherford SC. Obese and lean Zucker rats differ in preferences for sham-fed corn oil or sucrose. *Am J Physiol.* 1990; 259(6 Pt 2):R1093–5. [PubMed: 2260719]
- Hursh SR. The Wiley Blackwell Handbook of Operant and Classical Conditioning, First Edition, Chapter 12: Behavioral economics and the analysis of consumption of choice. 2014:275–305.
- Hursh SR, Roma PG. Behavioral economics and empirical public policy. *J Exp Anal Behav.* 2013; 99(1):98–124. [PubMed: 23344991]
- Hursh SR, Silberberg A. Economic demand and essential value. *Psychol Rev.* 2008; 115(1):186–98.
- Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci.* 2010; 13(5):635–41. [PubMed: 20348917]
- Kenny PJ. Common cellular and molecular mechanisms in obesity and drug addiction. *Nat Rev Neurosci.* 2011; 12:638–51. [PubMed: 22011680]
- Leonard WR. The global diversity of eating patterns: Human nutritional health in comparative perspective. *Physiol Behav.* 2014; 134:5–14. [PubMed: 24613505]

- Liang NC, Hajnal A, Norgren R. Sham feeding corn oil increases accumbens dopamine in the rat. *Am J Physiol Regul Integr Comp Physiol*. 2006; 291:R1236–9. [PubMed: 16763080]
- Marco A, Schroeder M, Weller A. Feeding and reward: Ontogenetic changes in an animal model of obesity. *Neuropharmacology*. 2012; 62(8):2447–2454. [PubMed: 22401956]
- McKenney RL, Short DK. Tipping the balance: The pathophysiology of obesity and type 2 diabetes mellitus. *Surg Clin North Am*. 2011; 91(6):1139–1148. [PubMed: 22054144]
- Philips MS, Liu Q, Hammond HA, Dugan V, Hey PJ, Caskey CJ, Hess JF. Leptin receptor missense mutation in the fatty Zucker rat. *Nat Genet*. 1996; 13(1):18–9. [PubMed: 8673096]
- Rasmussen EB, Huskinson SL. Effects of rimonabant on behavior maintained by progressive ratio schedules of sucrose reinforcement in obese Zucker (fa/fa) rats. *Behav Pharmacol*. 2008; 19(7): 735–42. [PubMed: 18797250]
- Rasmussen EB, Reilly W, Buckley J, Boomhower SR. Rimonabant reduces the essential value of food in the genetically obese Zucker rat: An exponential demand analysis. *Physiol Behav*. 2012; 105:734–741. [PubMed: 22019829]
- Rasmussen EB, Reilly W, Hillman C. Demand for sucrose in the genetically obese Zucker (fa/fa) rat. *Behav Processes*. 2010; 85(2):191–7. [PubMed: 20674704]
- Rissanen A, Hakala P, Lissner L, Mattlar CE, Koskenvuo M, Ronnema. Acquired preference especially for dietary fat and obesity: A study of weight-discordant monozygotic twin pairs. *International Journal of Obesity*. 2002; 26:973–977. [PubMed: 12080452]
- Scarpace PJ, Zhang Y. Leptin resistance: a predisposing factor for diet induced obesity. *Am J Physiol Regul Integr Comp Physiol*. 2009; 296(3):R493–500. [PubMed: 19091915]
- Stice E, Spoor S, Ng J, Zald DH. Relation of obesity to consummatory and anticipatory food reward. *Physiol Behav*. 2009; 1497(5):551–60. [PubMed: 19328819]
- Thanos PK, Michaelides M, Gispert JD, Pascau J, Soto-Montenegro ML, Desco M, Wang R, Wang GJ, Volkow ND. Differences in response to food stimuli in a rat model of obesity: in-vivo assessment of brain glucose metabolism. *Int J Obes*. 2008; 32(7):1171–9.
- Thanos PK, Michaelides M, Ho CW, Wang GJ, Newman AH, Heidbreder CA, Ashby CR Jr, Gardner EL, Volkow ND. The effects of two highly selective dopamine D3 receptor antagonists (SB-277011A and NGB-2904) on food self-administration in a rodent model of obesity. *Pharmacol Biochem Behav*. 2008; 89(4):499–507. [PubMed: 18329700]
- Thanos PK, Robinson LS, Robinson JK, Michaelides M, Wang GJ, Volkow ND. Obese rats with deficient leptin signaling exhibit heightened sensitivity to olfactory food cues. *Synapse*. 2013; 67(4):171–8. [PubMed: 23172699]
- Tomasi D, Volkow ND. Striatocortical pathway dysfunction in addiction and obesity: differences and similarities. *Crit Rev in Biochem and Molec Bio*. 2013; 48(1):1–19. [PubMed: 23173916]
- Volkow ND, Wang GJ, Fowler JS, Tomasi D, Baler R. Food and drug reward: overlapping circuits in human obesity and addiction. *Curr Top Behav Neurosci*. 2011; 11:1–24. [PubMed: 22016109]
- Volkow ND, Wang GJ, Tomasi D, Baler RD. The addictive dimensionality of obesity. *Biol Psychiatry*. 2013; 73(9):811–818. [PubMed: 23374642]
- Wang GJ, Volkow ND, Fowler JS. The role for dopamine in motivation for food in humans: implications for obesity. *Expert Opin. Ther. Targets*. 2002; 6:601–9. [PubMed: 12387683]
- Wellman PJ, Nation JR, Davis KW. Impairment of acquisition of cocaine self-administration in rats maintained on a high fat diet. *Pharmacol Biochem Behav*. 2007; 88(1):89–93. [PubMed: 17764729]

Highlights

- Obese and lean Zucker rats self-administered corn oil and cocaine.
- Corn oil was a more effective reinforcer in obese than in lean Zucker rats.
- The reinforcing effects of cocaine were similar between obese and lean Zucker rats.

Figure 1.

Summary of corn oil consumption. (A) Aggregated mean demand curves for corn oil in obese (closed symbols) and lean (open symbols) Zucker rats. (B) Mean $\pm$ SEM baseline corn oil consumption (i.e., FR1) in obese (closed bar) and lean (open bar) rats. (C) Essential Value of corn oil in obese (closed bar) and lean (open bar) rats. Data were derived from individual demand curves. *** $p < 0.01$.

Figure 2.

Summary of cocaine consumption. (A) Aggregated mean demand curves for cocaine in obese (closed symbols) and lean (open symbols) Zucker rats. (B) Mean $\pm$ SEM baseline cocaine consumption (i.e., FR1) in obese (closed bar) and lean (open bar) rats. (C) Essential Value of cocaine in obese (closed bar) and lean (open bar) rats. Data were derived from individual demand curves.