Published in final edited form as:

Physiol Behav. 2017 March 01; 170: 88–92. doi:10.1016/j.physbeh.2016.12.016.

Comparison of cocaine reinforcement in lean and obese Zucker rats: Relative potency and reinstatement of extinguished operant responding

E. Andrew Townsend and Kevin B. Freeman

Graduate Program in Neuroscience and Division of Neurobiology and Behavior Research, Department of Psychiatry and Human Behavior, The University of Mississippi, Medical Center, Jackson, MS 39216

Abstract

Aims—Evidence indicates that obese individuals exhibit alterations in brain-reward function that are anatomically and functionally similar to what has been observed in drug addicts, which could theoretically make obese individuals vulnerable to drug abuse and drug abusers vulnerable to overeating. However, few studies have investigated the cross-generalizability of these phenotypes. We recently reported that the reinforcing effectiveness (i.e., value) of a fat was greater in obese Zucker rats than in their lean counterparts, but found no differences in the reinforcing effectiveness of cocaine between groups, suggesting psychostimulant reinforcement is similar in lean and obese Zucker rats. However, it is unknown if other aspects of reinforcement such as cocaine's potency as a reinforcer or its reinstating effects differ in lean and obese Zucker rats.

Methods—The current study compared cocaine's potency as a reinforcer in lean and obese Zucker rats self-administering intravenous cocaine (0.06–1.0mg/kg/inj), and subsequently tested these subjects in cue- (light) and drug-primed (intraperitoneal cocaine; 10mg/kg) reinstatement of extinguished operant responding.

Results—All rats acquired cocaine self-administration and generated “inverted-U” dose-response functions. Following extinction of responding, the cue- and drug-primed increased lever-pressing in both groups (i.e., reinstatement). No significant differences in the reinforcing potency or reinstating effects of cocaine were observed as a function of obesity.

Conclusions—These results, combined with our previous observations, demonstrate that cocaine's reinforcing effects are comparable in lean and obese Zucker rats and do not support the hypothesis that obesity is associated with an altered reinforcing effect of psychostimulants.

Keywords

obesity; Zucker rat; cocaine; self-administration

Address all correspondence to: E. Andrew Townsend, Division of Neurobiology and Behavior Research, Department of Psychiatry and Human Behavior, The University of Mississippi Medical Center, Jackson, MS 39216, Phone: (601) 984-5743, Fax: (601) 984-5998, s52drew@gmail.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1. Introduction

Interest in studying the etiology of obesity within an addiction framework has increased in recent years (Hebebrand et al., 2014; Marcus and Wildes, 2014; Meule and Gearhardt, 2014). Evidence indicates that obese individuals exhibit alterations in brain-reward function that are similar to what has been observed in stimulant addicts (Burger and Stice, 2011; Michaelides et al., 2012; Tomasi and Volkow, 2013). Hypothetically, these changes cause increased consumption of highly palatable, energy-dense foods, which in turn perpetuates obesity (Volkow et al., 2013b). Obese humans rate foods that are high in fat and/or sugar as more pleasant than their non-obese counterparts (Drewnowski et al., 1985; Rissanen et al., 2002), and obese humans exhibit altered brain responsiveness to consumption of palatable foods relative to non-obese controls (Gearhardt et al., 2011). Moreover, areas of the brain responsible for motivation and reward that are activated by drug-associated cues in drug addicts are hyper-activated by food cues in the obese (Volkow, 2013a), further suggesting that drug addiction and overeating share common neuronal underpinnings.

However, despite this evidence, obese people and drug addicts do not appear to be universally vulnerable to both overeating and drug abuse. There is no evidence that obese individuals are more likely to abuse drugs or that drug addicts find palatable, energy-dense foods more reinforcing than non-addicts. In fact, some studies suggest that obesity and/or a history of eating high-fat or high-sugar foods may reduce the likelihood of taking drugs (e.g., Blum et al., 2012; Davis et al., 2008; Li et al., 2016; Simon et al., 2006; Wellman et al., 2007). For example, rats maintained on a high-fat diet exhibit reduced place preference to amphetamine and reduced acquisition of cocaine self-administration relative to rats maintained on a standard-chow diet (Davis et al., 2008; Wellman et al., 2007). Furthermore, obese humans are less likely to be diagnosed with substance use disorders, and Body Mass Index is inversely related to illicit drug use (Blum et al., 2012; Li et al., 2016; Simon et al., 2006). However, the supposition that obesity can reduce the likelihood of abusing drugs must take into account the possibility that differences in diet between obese and non-obese individuals could be affecting responsivity to drugs independent of obesity. Wellman et al. (2007) reported that rats maintained on a high-fat diet were less likely to acquire self-administration of cocaine, and this effect occurred in rats that became obese on the high-fat diet as well as those that did not. Thus, it may be the case that lower rates of drug abuse in the obese have less to do with the obese state, per se, and more to do with current diet and/or diet history. However, when using animal models, it is difficult to know the relative roles of diet history and obesity in altered reinforcement processes because calorie-dense foods like fat and sugar are typically used to induce obesity (e.g., Johnson and Kenny, 2010).

One way to study the effects of obesity on an endpoint without using a special diet is to use a spontaneous genetic model of obesity such as the Zucker rat strain (see Wang et al., 2014 for review). Obesity in the Zucker rat strain is caused by homozygotic expression of a mutant leptin receptor allele, which greatly diminishes the ability of leptin to bind to its receptor and terminate feeding behavior (Takaya et al., 1996). Animals expressing this mutant leptin receptor (i.e., obese Zucker rats) display hyperphagic feeding behaviors, hyperinsulinemia, and hyperlipidemia (Kobatake et al., 1989). In contrast, littermates that do

not express the mutant leptin receptor (i.e., lean Zucker rats) have relatively normal leptin signaling and exhibit growth curves that are comparable to outbred strains (Wang et al., 2014). A critical feature of the Zucker obesity model is that obesity is reliably induced through voluntary, hyperphagic consumption of standard chow (Wang et al., 2014). Thus, when comparing obese to lean Zucker rats, the study is not confounded by the groups having qualitatively different diet histories as is usually the case with diet-induced obesity models. This becomes an important feature of the model when examining the role of obesity in reinforcement processes because, as stated above, obesogenic foods affect responsivity to food and drug reinforcers independent of obesity (Davis et al., 2008; Wellman et al., 2007).

Recently, we examined the relative reinforcing effects of an orally-consumed fat (corn oil) and intravenous cocaine injections in lean and obese Zucker rats (Townsend et al., 2015). Using a behavioral economic demand approach, we determined that corn oil was a more effective reinforcer in obese than in lean rats (Townsend et al., 2015). However, while cocaine functioned as a reinforcer in all rats, its reinforcing effectiveness was comparable between the cohorts (Townsend et al., 2015). We concluded that obesity, as modeled in the Zucker rat, is associated with a greater reinforcing effect of fat, and that an enhanced value of fat may be a contributor to overeating in obese humans. However, our results with cocaine did not support the supposition that obesity is associated with alterations in the reinforcing effects of drugs. Rather, the similarity of cocaine self-administration between the groups suggested that obesity neither predisposes nor protects one from acquiring drug-taking behavior. However, our ability to make conclusions on this issue was limited by the fact that we only tested one dose of cocaine. Issues that remain to be investigated in lean and obese Zucker rats are cocaine's relative potency as a reinforcer and the ability of cocaine and cocaine-paired cues to reinstate extinguished responding previously maintained by cocaine injections.

The purpose of the current study was 1) to determine dose-response relations for cocaine self-administration in lean and obese Zucker rats, and 2) to investigate the relative effects of cocaine injections and cocaine-paired cues on reinstatement of extinguished operant responding previously maintained by cocaine injections. Based on the comparable levels of cocaine self-administration in Townsend et al. (2015), we hypothesized that cocaine's potency as a reinforcer and the reinstating effects of cocaine and its associated cues would be similar in lean and obese Zucker rats.

2. Method

2.1. Subjects

Eight lean and 8 obese male Zucker rats (Harlan Laboratories, New Jersey, USA) were used in the acquisition and dose-response portions of the experiment. Due to unsuccessful replacement catheter surgeries, 6 lean and 7 obese rats progressed to the subsequent extinction and reinstatement portions of the experiment. Rats were approximately 12 weeks of age at the outset of the study. Obesity in the Zucker rat is the consequence of homozygotic expression of an autosomal recessive mutation (i.e., *fa/fa*) of the leptin receptor, with renders obese Zucker rats relatively insensitive to leptin (Wang et al., 2014). Additionally, heterozygotes do not show a partial expression of the obese phenotype (Wang

et al., 2014). As such, rats were genotyped as either lean (i.e., *fa/Fa* or *Fa/Fa*) or obese (*fa/fa*) by Harlan Laboratories and initial weights ranged from 292–390g for lean rats and 430–540g for obese rats. Animals were pair-housed (lean with lean and obese with obese) and tested 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 dark 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 standard modular operant test chambers (Med-Associates, St. Albans, VT, USA) were used for all procedures. Each chamber was equipped with two retractable levers, each with a corresponding white stimulus light mounted above. Cocaine injections were delivered through 30-ml plastic syringes that were seated in infusion pumps located outside of the chamber (Razel Scientific, St. Albans, VT, USA). Polyethylene tubing connected the cocaine-filled syringe 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 mid-scapular area of the rat (see Surgery). Operant chambers were enclosed in ventilated sound-attenuating chambers (Med-Associates, St. Albans, VT, USA). Test sessions lasted 2-h and were conducted 7-d per week. A desktop computer equipped with Med-Associates software (Med-PC for Windows; St. Albans, VT, USA) controlled all experimental conditions and recorded data.

2.3. Surgery

Rats were implanted with intravenous catheters as described previously (Townsend et al., 2015). 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 (100 U/ml). Catheters were considered patent if ataxia was apparent within 3-s of injection. If a catheter was considered non-functional during the self-administration portion of the experiment, a new catheter was implanted into the left-jugular vein and the animal continued in the experiment. Two rats (one lean, one obese) were successfully implanted with left jugular catheters and continued in the experiment. Catheter patency was also verified immediately following the last cocaine self-administration session of each animal.

2.4. Procedure

2.4.1. Acquisition of Stable Cocaine Self-Administration—After allowing five days of post-surgical recovery, rats were placed into operant chambers for daily self-administration sessions. Initiation of test sessions was signaled by extension of the retractable levers. The left response lever was deemed the “active” lever and the right lever was deemed the “inactive” lever. A sufficient number of responses on the active lever resulted in retraction of the active lever, a cocaine injection (0.5 mg/kg), and a 5-s cue light presentation. Responses on the inactive lever were also recorded but had no programmed

consequences. The initial response requirement on the active lever was one lever-press (i.e., FR1 schedule of reinforcement). After a rat earned at least ten cocaine injections for three consecutive days, the schedule of reinforcement was raised to FR5. Subsequent to this change, self-administration was considered stable when the injections earned over three serial days were within 20% of the three-session mean with no upward or downward trends. The number of injections earned on the final day of acquisition was used to represent cocaine consumption at 0.5mg/kg/inj in dose-response comparisons.

2.4.2. Cocaine Dose-Response Testing—After stable cocaine intake was determined for 0.5 mg/kg/inj, cocaine intake was tested at a variety of doses (0.0625, 0.125, 0.25, and 1.0 mg/kg/inj), with the aim of completing a bi-phasic, “inverted-U” dose-response function for each subject. Programmed consequences of this portion of the experiment were identical to those in place for the acquisition phase. Cocaine dose (mg/kg) was rendered for each subject by adjusting the infusion time based on body weights (determined weekly). Each dose of cocaine was tested for three consecutive sessions, and the third session, regardless of the intake on the first two days, was used to represent consumption for that dose. Initial doses of 0.125 and 0.25 mg/kg/inj were tested in a counterbalanced order. If an “inverted-U” dose-response function was not apparent after testing these doses (i.e., 0.25 mg/kg/inj was not the peak dose), a dose of either 0.0625 or 1.0 mg/kg/inj was chosen based on individual consumption of the previous doses (e.g., if the number of injections peaked at 0.5 mg/kg/inj, the higher dose of 1.0 mg/kg/inj was tested). Notably, because the drug-paired cue light was used to test cue-induced reinstatement in these subjects (see below), we made the decision not to test saline in this series so that the drug-associated cue was never paired with a non-drug condition. We argue that concerns over the omission of a saline condition are mitigated by 1) the inclusion of sufficient doses to render ascending and descending limbs on “inverted-U” dose-response functions in each subject (i.e., dose-dependent drug taking behavior), and 2) the fact that the issue of whether or not cocaine is a reinforcer is not in question because that has been well established in rats, including obese and lean Zuckers (Townsend et al., 2015). Once dose-response functions were determined, self-administration was re-established at the training dose (0.5 mg/kg/inj) in all rats until the same stability criteria described in acquisition were met.

2.4.3. Extinction of Lever-Pressing Behavior—After rats re-established stable intake of cocaine, they were tested in no fewer than seven daily extinction sessions. As in cocaine self-administration sessions, the initiation of an extinction session was signaled by the extension of both levers and responses were recorded, but had no programmed consequences. A rat was considered to have completed extinction if active lever-pressing behavior was reduced to fewer than 25 on days 6 and 7. If responding on days 6 and 7 were higher than criteria, additional extinction sessions were tested until lever-pressing behavior was lower than 25 presses for two consecutive days.

2.4.4. Cue-Induced Reinstatement—Once lever-pressing behavior was adequately extinguished, rats were tested for cue-induced reinstatement. Initiation of the reinstatement session was signaled by simultaneous extension of the levers and a 5-s presentation of the

cue light previously paired with cocaine injections. Subsequent active lever presses were recorded and resulted in 5-s light presentations.

2.4.5. Post-Cue Extinction—After cue-induced reinstatement, rats were re-tested with the same extinction program as described above. However, the minimum number of sessions for extinction was lowered from 7 to 3. If the rat emitted fewer than 25 active lever responses on days 2 and 3 of this round of extinction, the animal progressed to the next phase of the experiment. If the number of responses was greater than criteria, additional extinction sessions were tested until lever-pressing behavior was lower than 25 for two consecutive days.

2.4.6. Cocaine-Primed Reinstatement—This portion of the experiment measured the number of unreinforced lever-presses following an intra-peritoneal injection of cocaine solution (10 mg/kg). After the cocaine injection, rats were immediately placed into the operant chamber and tested using the same parameters as the extinction program. Thus, lever-presses were recorded and had no programmed consequences.

2.5. Data Analysis

The rates of stable acquisition of cocaine self-administration between lean and obese rats were compared using a log-rank (Mantel-Cox) survival test. Cocaine dose-response comparisons were limited to the three “core” doses to which all subjects were exposed (i.e., 0.125, 0.25, and 0.5 mg/kg/inj). Within this dose range, both the number of earned injections and the milligrams consumed were each compared between lean and obese rats with repeated measures 2-way analysis of variance (ANOVA) tests. The number of active lever presses across the first seven extinction sessions were also compared between groups using a repeated measures 2-way ANOVA.

To determine if rats reinstated lever-pressing behavior in the presence of either the drug-associated cue or a drug-prime, the average number of active lever-presses during the last two days of extinction were compared to the number of active lever-presses emitted during a single reinstatement condition within each group using paired *t*-tests. To determine if the number of responses emitted during a reinstatement condition (i.e., cue-induced or drug-primed) differed between groups, active lever-presses during a reinstatement condition were compared between groups using unpaired *t*-tests.

2.6. 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. Results

All subjects acquired stable cocaine self-administration. Rates of acquisition were similar between the lean and obese rats (Figure 1) as evidenced by a lack of an effect of group on a survival analysis ($\chi^2 = 0.068$; $df = 1$; $p = 0.79$). When the number of earned infusions were plotted across subjects as a function of dose (Figure 2, top panel), “inverted-U” dose-

response functions were rendered for both groups. When the number of injections earned were compared within the 0.125, 0.25, and 0.5 mg/kg dose range, a 2-way ANOVA did not detect an effect of dose ($F[2,30] = 2.69, p = 0.084$), group ($F[1,15] = 1.10, p = 0.31$), or a dose $\times$ group interaction ($F[2,30] = 0.62, p = 0.55$), suggesting that cocaine's potency as a reinforcer was comparable between the lean and obese groups. Additionally, comparison of the milligrams earned within the same dose range (Figure 2, bottom panel) revealed no effects of group ($F[1,15] = 0.082, p = 0.78$) or a group $\times$ strain interaction ($F[2,30] = 2.16, p = 0.13$), but an effect of dose was detected ($F[2,30] = 28.48, p < 0.0001$).

When cocaine and the associated visual stimuli were no longer available, lever-pressing behavior decreased similarly in both groups over the first seven days of extinction ($F[6,66] = 16.35, p < 0.0001$) (Figure 3), although no differences in this effect were observed between the lean and obese animals ($F[1,11] = 1.85, p = 0.20$). As shown in Figure 4, reintroduction of the drug-paired stimulus light resulted in a significant increase in the number of active lever presses in both lean ($t = 7.99, df = 5, p = 0.0005$) and obese ($t = 2.62, df = 6, p = 0.039$) rats, and the magnitude of this response was similar between groups ($t = 0.033, df = 11, p = 0.97$). Similarly, a non-contingent cocaine injection (10 mg/kg) resulted in a significant increase in the number of active lever presses in both lean ($t = 5.07, df = 5, p = 0.0039$) and obese ($t = 3.25, df = 6, p = 0.018$) rats, and the magnitude of the response was similar between groups ($t = 1.61, df = 11, p = 0.14$).

4. Discussion

The main findings of the present study were that acquisition of cocaine self-administration, cocaine's potency as a reinforcer, and the reinstating effects of cocaine and a cocaine-paired stimulus were all similar in lean and obese Zucker rats. These results are consistent with our previous findings in which lean and obese Zucker rats self-administered similar amounts of a dose of cocaine at a low response requirement and exhibited similar elasticities of demand when that dose of cocaine was tested in a behavioral economic procedure (Townsend et al., 2015). When taken together, Townsend et al. (2015) and the current data demonstrate that obesity as modeled in the Zucker rat does not render a change in the reinforcing effects of cocaine. These data, taken together with previous reports of high fat diets decreasing the abuse related effects of psychostimulants (e.g., Bluml et al., 2012; Davis et al., 2008; Li et al., 2016; Simon et al., 2006; Wellman et al., 2007), suggest an obese phenotype is not necessarily associated with an alteration in drug reinforcement. Rather, exposure to obesogenic diets appear to alter mesocorticolimbic functionality (Naef et al., 2015), which may result in differential sensitivity to drugs of abuse.

A range of cocaine doses were tested in self-administration to capture the ascending and descending limbs of cocaine's characteristic "inverted-U" dose-response function in each animal, and when averaged together across subjects, there were no significant differences between lean and obese rats in cocaine self-administration at any dose tested. This finding demonstrates that cocaine's potency as a reinforcer is comparable in lean and obese Zucker rats. Interestingly, when self-administration was plotted as a function of mg of intake (i.e., independent of body weight; Figure 2, lower panel), the absolute intake of cocaine was shown to be very similar in the lean and obese rats, despite their well-characterized

differences in body weight and fat composition (Aleixandre de Artinano and Miguel Castro, 2009; Bray, 1997; Chua et al., 1996). These results raise the intriguing possibility that body mass, at least in terms of relative adiposity, may not be a significant factor in dose selection for stimulant abusers. In terms of future study designs, the fact that the lean and obese rats self-administer similar absolute amounts of cocaine indicates that dosing for individual subjects may need to be delivered irrespective of body weight, as heavier animals may appear to self-administer fewer injections when in fact they are taking amounts that are comparable to their lean counterparts.

Acquisition of cocaine self-administration has been reported to be impaired in rats maintained on a high-fat diet (Wellman et al., 2007). However, as stated above, not all of the rats in the high-fat diet group in the Wellman et al. report became obese. Wellman et al. concluded that the differences seen in cocaine self-administration between high-fat diet- and control-fed rats were due to the diet itself and not necessarily differences in weight gain. The fact that the lean and obese Zucker rats in the current report were comparable in cocaine self-administration, including acquisition, supports the conclusions of Wellman et al. because both groups were fed the same standard diet. Similarly, a recent report found that ob/ob mice with deficient leptin-receptor signaling were no different than their lean, wild-type counterparts in self-administration of a dose of cocaine (0.5 mg/kg/inj) under fixed and progressive-ratio schedules of reinforcement (Muelbl et al., 2016), and these animals also had the same standard diet histories. In addition to changes in cocaine self-administration, exposure to a high-fat diet has been reported to enhance the locomotor-stimulating effects of cocaine in adolescent male (Baladi et al., 2012), but not adult male or female (Baladi et al., 2012; Serafine et al., 2014) rats. Thus, it is possible that the lower rates of drug abuse reported in obese humans (Bluml et al., 2012; Li et al., 2016; Simon et al., 2006) may have more to do with differences in diet selection than body mass/adiposity.

In recent years, there has been much discussion regarding the potential of common mechanisms underlying drug addiction and obesity (DiLeone et al., 2012; Kenny, 2011; Volkow et al., 2013a). A growing body of research has demonstrated that the consumption of highly palatable, energy-dense foods causes brain activity in reinforcement-related areas similar to drugs of abuse, and that drug addicts and obese individuals show similar plasticity changes in these areas (Kenny, 2011; Volkow et al., 2013a). One implication is that these common mechanisms may confer vulnerability across the addiction phenotypes (i.e., from food to drugs and vice versa). However, the current data, when taken with our previous report (Townsend et al., 2015), do not support this supposition. Our findings indicate that obesity, as modeled in the Zucker strain, is associated with an enhanced reinforcing effect of fat but not a drug of abuse (Townsend et al., 2015; current report). This reinforcer-specific alteration in motivation suggests that, in addition to overlaps, there are also key differences in neuroadaptations associated with obesity and drug abuse that underlie their respective behavioral pathologies.

Acknowledgments

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 Talal Ahmed, Steven Ross, and Jacob Smith.

References

- Aleixandre de Artinano A, Miguel Castro M. Experimental rat models to study the metabolic syndrome. *Br J Nutr.* 2009; 102:1246–1253. [PubMed: 19631025]
- Baladi MG, Koek W, Aumann M, Velasco F, France CP. Eating a high fat chow enhances the locomotor-stimulating effects of cocaine in adolescent and adult female rats. *Psychopharmacology.* 2012; 222:447–457. [PubMed: 22418731]
- Bluml V, Kapusta N, Vyssoki B, Kogoj D, Walter H, Lesch OM. Relationship between substance use disorder and body mass index in young males. *Am J Addict.* 2012; 21:72–72. [PubMed: 22211349]
- Bray GA. The Zucker-fatty rat: a review. *Federation Proceedings.* 1977; 36:148–153. [PubMed: 320051]
- Burger KS, Stice E. Variability in reward responsively and obesity: evidence from brain imaging studies. *Curr Drug Abuse Rev.* 2011; 4:182–189. [PubMed: 21999692]
- Chua SC Jr, Chung WK, Wu-Peng XS, Zhang Y, Liu SM, Tartaglia L, Leibel RL. Phenotypes of mouse diabetes and rat fatty due to mutations of the OB (leptin) receptor. *Science.* 1996; 271:994–996. [PubMed: 8584938]
- Davis JF, Tracy AL, Schurdak JD, Tschop MH, Lipton JW, Clegg DJ, Benoit SC. Exposure to elevated levels of dietary fat attenuates psychostimulant reward and mesolimbic turnover in the rat. *Behav Neurosci.* 2008; 122:1257–1263. [PubMed: 19045945]
- DiLeone RJ, Taylor JR, Picciotto MR. The drive to eat: comparisons and distinctions between mechanisms of food reward and drug addiction. *Nat Neurosci.* 2012; 15:1330–1335. [PubMed: 23007187]
- Drewnowski A, Brunzell JD, Sande K, Iverius PH, Greenwood MR. Sweet tooth reconsidered: taste responsiveness in human obesity. *Physiol Behav.* 1985; 35:617–622. [PubMed: 4070436]
- Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Arch Gen Psychiatry.* 2011; 68:808–816. [PubMed: 21464344]
- Hebebrand J, Albayrak O, Adan R, Antel J, Dieguez C, de Jong J, Leng G, Menzies J, Mercer JG, Murphy M, van der Plasse G, Dickinson SL. “Eating addiction”, rather than “food addiction”, better captures addictive-like eating behavior. *Neurosci Biochem Rev.* 2014; 47:295–306.
- Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nat Neurosci.* 2010; 13:635–641. [PubMed: 20348917]
- Kenny PJ. Common cellular and molecular mechanisms in obesity and drug addiction. *Nat Rev Neurosci.* 2011; 12:638–651. [PubMed: 22011680]
- Kobatake T, Matsuzawa Y, Tokunaga K, Fujioka S, Kawamoto T, Keno Y, Inui Y, Odaka H, Matsuo T, Tarui S. Metabolic improvements associated with a reduction of abdominal visceral fat caused by a new alpha-glucosidase inhibitor, AO-128, in Zucker fatty rats. *Int J Obes.* 1989; 13:147–154. [PubMed: 2663746]
- Li J, Yang C, Davey-Rothwell M, Latkin C. Associations between body weight status and substance use among African American women in Baltimore, Maryland: The CHAT study. *Subst Use Misuse.* 2016; 51:669–681. [PubMed: 27050238]
- Marcus MD, Wildes JE. Disordered eating in obese individuals. *Curr Opin Psychiatry.* 2014; 27:443–447. [PubMed: 25247456]
- Meule A, Gearhardt AN. Food addiction in the light of DSM-5. *Nutrients.* 2014; 6:3653–3671. [PubMed: 25230209]
- Michaelides M, Thanos PK, Volkow ND, Wang GJ. Translational neuroimaging in drug addiction and obesity. *ILAR J.* 2012; 53:59–68. [PubMed: 23520600]
- Muelbl MJ, Nawarawong NN, Clancy PT, Nettesheim CE, Lim YW, Olsen CM. Responses to drugs of abuse and non-drug rewards in leptin deficient ob/ob mice. *Psychopharmacology.* 2016; 233:2799–2811. [PubMed: 27256358]
- Naef L, Pitman KA, Borgland SL. Mesolimbic dopamine and its neuromodulators in obesity and binge eating. *CNS Spectr.* 2015; 20:574–583. [PubMed: 26514168]

- Rissanen A, Hakala P, Lissner L, Mattlar CE, Koskenvuo M, Ronnema T. Acquired preference especially for dietary fat and obesity: a study of weight-discordant monozygotic twin pairs. *Int J Obes Relat Metab Disord*. 2002; 26:973–977. [PubMed: 12080452]
- Serafine KM, Bentley TA, Grenier AE, France CP. Eating high fat chow and the behavioral effects of direct-acting and indirect-acting dopamine receptor agonists in female rats. *Behav Pharmacol*. 2014; 25:287–295. [PubMed: 24949571]
- Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry*. 2006; 63:824–830. [PubMed: 16818872]
- Takaya K, Ogawa Y, Isse N, Okazaki T, Satoh N, Masuzaki H, Mori K, Tamura N, Hosoda K, Nakao K. Molecular cloning of rat leptin receptor isoform complementary DNAs-identification of a missense mutation in Zucker Fatty (*fa/fa*) rats. *Biochem Biophys Res Commun*. 1996; 225:75–83. [PubMed: 8769097]
- Tomasi D, Volkow ND. Striatocortical pathway dysfunction in addiction and obesity: differences and similarities. *Crit Rev Biochem Mol Biol*. 2013; 48:1–19. [PubMed: 23173916]
- Townsend EA, Beloate LN, Huskinson SL, Roma PG, Freeman KB. Corn oil but not cocaine, is a more effective reinforcer in obese than in lean Zucker rats. *Physiol Behav*. 2015; 143:136–141. [PubMed: 25744935]
- Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev*. 2013a; 14:2–18. [PubMed: 23016694]
- Volkow ND, Wang GJ, Tomasi D, Baler RD. The addictive dimensionality of obesity. *Biol Psychiatry*. 2013b; 72:811–818.
- Wang B, Chandrasekera PC, Pippin JJ. Leptin- and leptin receptor-deficient rodent models: relevance for human type 2 diabetes. *Cur Diabetes Rev*. 2014; 10:131–145.
- 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; 88:89–93. [PubMed: 17764729]

Highlights

The reinforcing potency of cocaine is similar between lean and obese Zucker rats.

The reinstating effects of a cocaine-associated light stimulus and cocaine itself are similar in lean and obese Zucker rats.

Figure 1. Survival plot representation of acquisition of stable cocaine self-administration in lean (open symbols) and obese (closed symbols) Zucker rats.

Figure 2.

Sensitivity to the reinforcing effects of cocaine in lean (open symbols) and obese (closed symbols) Zucker rats. (Upper panel) Mean number of cocaine injections earned per session in lean (open symbols) and obese (closed symbols) Zucker rats. (Lower panel) Mean number of cocaine milligrams earned per session in lean (open symbols) and obese (closed symbols) Zucker rats. Numbers in parentheses indicate the number of subjects that experienced a particular dose not experienced by all subjects. Error bars represent one standard error of the mean (SEM).

Figure 3. Extinction of previously reinforced operant responding plotted as the mean number of active lever-presses as a function of session in lean (open symbols) and obese (closed symbols) Zucker rats. Error bars represent one standard error of the mean (SEM).

Figure 4.

Reinstatement of extinguished operant responding following reintroduction of either a drug-paired stimulus light or cocaine (lean: $n = 6$, obese: $n = 7$). (Left) Number of active lever-presses under extinction (lean: diagonal bar; obese: hatched bar) and cue-induced reinstatement (lean: open bar, obese: closed bar) conditions. (Right) Number of active lever-presses under extinction (lean: diagonal bar, obese: hatched bar) and cocaine-primed reinstatement (lean: open bar, obese: closed bar) conditions. Error bars represent one standard error of the mean (SEM), and asterisks indicate a significant difference between extinction and reinstatement within a condition, $p < 0.05$.