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

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HIGHLIGHTS

- Although previous studies have reported increases in measures of food reinforcement in Zucker rats, it appears that cocaine reinforcement is unaltered in this strain.
- Acquisition of stable cocaine self-administration was similar between lean and obese Zucker rats.
- 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.

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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-generality 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 (0.06–1.0 mg/kg/inj), and subsequently tested these subjects in cue- (light) and drug-primed (intraperitoneal cocaine; 10 mg/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-primes 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.

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1. Introduction

Interest in studying the etiology of obesity within an addiction framework has increased in recent years [11,16,17]. Evidence indicates that obese individuals exhibit alterations in brain-reward function that are similar to what has been observed in stimulant addicts [5,18,25]. Hypothetically, these changes cause increased consumption of highly palatable, energy-dense foods, which in turn perpetuates obesity [28]. Obese humans rate foods that are high in fat and/or sugar as more pleasant than their non-obese counterparts [9,21], and obese humans exhibit altered brain responsiveness to consumption of palatable foods relative to non-obese controls [10]. 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 [27], further suggesting that drug addiction and overeating share common neuronal underpinnings.

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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., [3,7,15,23,30]). 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 [7,30]. Furthermore, obese humans are less likely to be diagnosed with substance use disorders, and Body Mass Index is inversely related to illicit drug use [3,15,23]. 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. [30] 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., [12]).

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 [29] 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 [24]. Animals expressing this mutant leptin receptor (i.e., obese Zucker rats) display hyperphagic feeding behaviors, hyperinsulinemia, and hyperlipidemia [14]. 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 [29]. A critical feature of the Zucker obesity model is that obesity is reliably induced through voluntary, hyperphagic consumption of standard chow [29]. 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 [7,30].

Recently, we examined the relative reinforcing effects of an orally-consumed fat (corn oil) and intravenous cocaine injections in lean and obese Zucker rats [26]. Using a behavioral economic demand approach, we determined that corn oil was a more effective reinforcer in obese than in lean rats [26]. However, while cocaine functioned as a reinforcer in all rats, its reinforcing effectiveness was comparable between the cohorts [26]. 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. [26], 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, which renders obese Zucker rats relatively insensitive to leptin [29]. Additionally, heterozygotes do not show a partial expression of the obese phenotype [29]. 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 to 390 g for lean rats and 430–540 g 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 h. 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 10-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 [26]. 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.