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Corn oil, but not cocaine, is a more effective reinforcer in obese than in lean Zucker rats

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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.

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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.

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1. Introduction

Rates of obesity in the United States have increased 40–50% in the past twenty years [23]. Over the same time period, measures of physical activity have decreased and caloric intake has risen, indicating an increase in non-homeostatic eating [23]. Consuming excessive amounts of energy-dense, highly palatable foods contributes to obesity onset and maintenance [12]. 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 [39] 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 [9,31]. Furthermore, obese subjects have altered brain activation in response to palatable food anticipation and consumption [15]. 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 [4,6,11,25,41]. 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 [27]. 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 [34]. 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 [16]. Furthermore, obese Zucker rats achieve higher breakpoints on a progressive-ratio (PR) schedule of reinforcement for grain pellets than their lean counterparts [16]. Notably, group differences in food-pellet self-administration disappear when Zucker

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rats are food-restricted [35], 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 [28]. Furthermore, demand elasticity for sucrose pellets in obese and lean Zucker rats is comparable [30]. 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 [4]. 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 [17].

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 [20]. 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 [20] Exponential Model of Demand, which defines a reinforcer's strength by quantifying its sensitivity to price (demand elasticity; see [18–20]). 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, FR 1). Given that obese Zucker rats consume food at a higher rate than their lean counterparts under both ad lib and operant conditions [4,16,30], 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 [7,22,38,39]. However, it is unknown if altered responsiveness to food reward related to obesity can generalize to a drug of abuse. The behavioral economic approach is well suited for comparing food and drug reinforcement between rat strains (e.g., [5]). 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 h. 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 was delivered through polyethylene tubing and 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 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's back (see the Surgery section). 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 20 g 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 10 s 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.