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Rimonabant reduces the essential value of food in the genetically obese Zucker rat: An exponential demand analysis

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ABSTRACT

Research on free-food intake suggests that cannabinoids are implicated in the regulation of feeding. Few studies, however, have characterized how environmental factors that affect food procurement interact with cannabinoid drugs that reduce food intake. Demand analysis provides a framework to understand how cannabinoid blockers, such as rimonabant, interact with effort in reducing demand for food. The present study examined the effects rimonabant had on demand for sucrose in obese Zucker rats when effort to obtain food varied and characterized the data using the exponential ("essential value") model of demand. Twenty-nine male (15 lean, 14 obese) Zucker rats lever-pressed under eight fixed ratio (FR) schedules of sucrose reinforcement, in which the number of lever-presses to gain access to a single sucrose pellet varied between 1 and 300. After behavior stabilized under each FR schedule, acute doses of rimonabant (1–10 mg/kg) were administered prior to some sessions. The number of food reinforcers and responses in each condition was averaged and the exponential and linear demand equations were fit to the data. These demand equations quantify the value of a reinforcer by its sensitivity to price (FR) increases. Under vehicle conditions, obese Zucker rats consumed more sucrose pellets than leans at smaller fixed ratios; however, they were equally sensitive to price increases with both models of demand. Rimonabant dose-dependently reduced reinforcers and responses for lean and obese rats across all FR schedules. Data from the exponential analysis suggest that rimonabant dose-dependently increased elasticity, i.e., reduced the essential value of sucrose, a finding that is consistent with graphical depictions of normalized demand curves.

1. Behavioral economics and food consumption

Behavioral economics is an area that merges principles of economics with experimental psychology, and has been used in the last three decades to model various health-related behaviors, including substance abuse [1,2] and obesity [3–5]. Consumer demand, one area of behavioral economics, assumes that the value of a commodity or outcome, such as food (or other reinforcers, such as drugs of abuse) is determined by the effort required to obtain it (see [6–10]). Effort is often quantified as the number of lever presses (via a fixed ratio schedule) required to earn a single reinforcer, e.g., a single food pellet. Simply stated, the more a single food pellet costs in terms of effort, the less it is consumed. Indeed, the relation between consumption of reinforcers and effort (price) has been mathematically characterized using the linear demand model [11,12]. A more recent model [13] characterizes demand as a single parameter — the exponential decay of the reinforcer as a function of unit price:

$$\log Q = \log Q_0 + k\left(e^{-\alpha Q P} - 1\right) \quad (1)$$

Here, Q refers to the number of reinforcers earned under a fixed ratio schedule (or price, P). Q_0 refers to consumption (number of reinforcers earned) at the lowest price (y-intercept). The free parameter α refers to the essential value of the reinforcer and is the value of exponential decay that describes sensitivity to price increases (also called elasticity). The parameter k refers to the range of values of the y-axis in log units. The equation, then, suggests that the number of reinforcers earned can be described by a slope that positively accelerates in a decreasing fashion as a function of price.

One advantage of the demand curve is that it provides a fuller characterization of the value of the reinforcer. If one considers how many food reinforcers are consumed at low prices *only* (such as research conducted on free food intake, for example), a mischaracterization of the value of the reinforcer is likely. For example, Rasmussen and colleagues [5] reported that obese Zucker rats consumed more sucrose pellets than lean controls when they were available at lower prices (fixed ratio values 1 through 50), but they were equally sensitive to higher price

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increases (i.e., had similar elasticity values compared to lean rats) when the full demand curve was examined. These data suggested that genetic variation that contributed to food value depended on how easily accessible sucrose was. Information such as this may be overlooked when only easily accessible food is used in studies on food intake.

2. Cannabinoids and food consumption

The endocannabinoid system, especially the CB1 receptor, is well established in terms of its role in feeding and hyperphagia. For example, endogenous ligands, such as 2-arachidonoyl glycerol (2-AG) or anandamide, as well as exogenous compounds, like delta-9 tetrahydrocannabinol (THC) or WIN 55,212-2, increase food intake by enhancing activity at the CB1 receptor [14–22] even when the organism is not food deprived, suggesting that at least one behavioral mechanism affected by cannabinoid activity is enhancement of food reward.

Cannabinoid CB1 receptor antagonists and inverse agonists, such as rimonabant, AM 4113, and AM251 (e.g., [23–25]) have drawn attention as drugs that can be used to treat behavioral disorders involved with overeating, such as obesity, by reducing food intake (see [26,27] for reviews). Rimonabant is probably the most well researched of these drugs to date, and indeed has been shown to reduce free food intake in animal studies [28–37], as well as reduce weight in clinical trials studies with obese humans [38–43]. Though rimonabant has side effects that have called into question its application for weight loss [44,45], the cannabinoid drug class is still of interest in treating disorders in which excessive contact with a reinforcing stimulus, such as food or drugs, is relevant [26,45–48]. Therefore, it is of interest that scientists and practitioners understand how the cannabinoid drug class, especially those drugs that block the CB1 receptor, interact with behavior related to food (and drug) procurement.

Many of the studies on cannabinoids' ability to alter food consumption center on free-food intake (e.g., [31,46,49–52], in which a rat emits a small amount of behavior (e.g., moving toward the food aperture) in a home cage in which a plentiful amount of food is readily available. Other studies in which food is made contingent upon a more effort-based schedule of reinforcement have shown that CB1 blockers reduce food-motivated behavior [21,36]. While these studies identify a behavioral mechanism (i.e., CB1 blockers reduce the reinforcing properties of food), they also raise questions about how cannabinoid antagonists may interact with the environmental arrangement of food. Rasmussen and Huskinson [36] found, for example, that 3–10 mg/kg of rimonabant reduced free-food intake in lean and obese Zucker rats by 25%, but when food was placed on a progressive ratio (PR) schedule of reinforcement, in which the response-cost for a food pellet increases within session with each food pellet earned, the effects of rimonabant were stronger; that is behavior was reduced by about 45%. The authors suggested that higher effort arrangements of food (i.e., PR schedules) may have a stronger interaction with rimonabant compared to lower effort environments (e.g., free food environments). A study that would examine drug effects across a range of efforts may answer questions about this relation.

3. The present study

If a drug such as rimonabant is purported to reduce ingestive behavior by reducing the reinforcing properties of food, it may do so in a manner that is environmentally specific, e.g., when response costs are high. The present study was designed to further examine the mechanism involved in rimonabant, in terms of reducing food intake by comparing dose-related consumption across different response requirements as a primary analysis. As a secondary analysis, we wanted to describe the data using the exponential demand analysis to determine if it would characterize the data well in this context. The exponential demand analysis has been used in other studies to assess the effects of deprivation on the reinforcing properties of drugs (e.g., [53]), as well as to make comparisons between the relative "value" of food and drugs [54, 55]; however, no studies to date have used the exponential demand analysis to describe the effects of drugs on altering food reinforcer efficacy. Therefore, this study would represent the first use of the exponential demand model in this context.

The present study also compared rimonabant-related effects in the obese and lean Zucker rat (*fa/fa*). The obese Zucker is a well-established genetic model of obesity and has been used for over 50 years to model health-related aspects of obesity, such as hypertension [56,57] and diabetes [58]. Its two homozygous *fa* "fatty" alleles are associated with impaired leptin signaling, which results in faulty inhibition of appetite-stimulating signals, such as neuropeptide Y (e.g., [59,60]) and endocannabinoids, such as anandamide [18], resulting in hyperphagia. Obese Zuckers also have higher cannabinoid levels in specific brain regions related to food regulation [18,61] which may be linked to sensitivity to cannabinoids that have been demonstrated in other studies [36,62]. As such, differences in rimonabant-induced changes in demand would be expected between lean and obese rats.

4. Material and methods

4.1. Subjects

Twenty-nine male Zucker rats ($n=15$ control, *Fa/fa* or *Fa/Fa*; $n=14$ obese, *fa/fa*) were procured from Harlan (Livermore, CA, USA) at approximately three weeks of age. Upon arrival, they were housed individually in clear, plexiglass home cages and maintained on a 12 h light:dark cycle (lights on at 7 a.m.). All rats had *ad libitum* access to food (Purina® grain-based rodent pellets) and water for eight weeks before experimental sessions began.

After eight weeks of free-feeding, rats were allowed to free-feed for a 2 h period 21 h prior to each experimental session to establish food as a reinforcer. This procedure leads to lean and obese Zuckers eating about 2.6% of their body weights during the free-feed sessions [5,36,62,63]. A two-hour free-feed period prevents rapid excessive weight gain in the Zucker rat, which can lead to health problems. At the time of operant testing for the current experiment, lean rats ranged in weight from 252 to 327 g and obese rats ranged from 415 to 507 g.

4.2. Apparatus

Seven Coulbourn® Habitest (Coulbourn Instruments, Whitehall, PA, USA) standard rat operant chambers were used for data collection. Each chamber contained two levers on the right side wall panel that were situated 5 cm from the bottom of a grid floor. Under programmed contingencies, a 45-mg sucrose pellet (95% sucrose; TestDiet®, Richmond, IN, USA) was dropped into a collection area above the floor that was centered between the two levers. The chamber was also equipped with a 28-V houselight that was situated 13 cm above the food dispenser, as well as a speaker that generated white noise, which was located in the upper left corner of the left side wall panel. In addition, a 5 cm × 5 cm fan was situated in the upper right corner of the left wall. Each chamber resided within a sound-attenuating cubicle. Graphic State® software (Coulbourn Instruments, Whitehall, PA, USA) on a Windows-based computer controlled all reinforcement contingencies and data collection with 0.01-s resolution. Computers and software were located in a room adjacent to the room containing the chambers. Experimental sessions were conducted from 9:00 a.m. to 2:00 p.m. at the same time (±15 min) from Monday to Friday. The time at which the rats were assigned to each session was counterbalanced across group (i.e., there were an equal number of lean and obese rats in the morning sessions and afternoon sessions).

4.3. Drug

Rimonabant (National Institute of Mental Health Chemical Synthesis and Drug Supply Program) was dissolved in a 1:1:18 ethanol (Sigma),