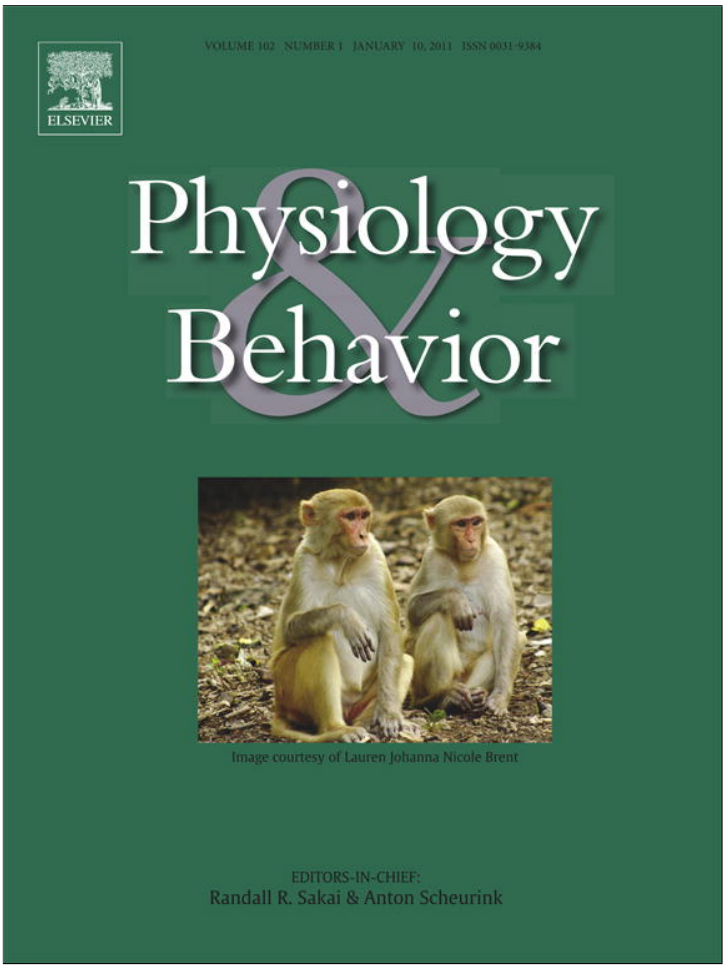

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Rimonabant reduces the essential value of food in the genetically obese Zucker rat: An exponential demand analysis

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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),

Cremaphor (Sigma), and saline solution (1 ml/kg) and was administered acutely via *i.p.* injection 1 h prior to the start of an experimental session, which ensures a peak dose is reached at the beginning of the session. Doses ranged between 1 and 10 mg/kg. Saline vehicle injections (1 ml/kg) were also administered *i.p.* prior to the beginning of some experimental sessions.

4.4. Procedures

4.4.1. Lever-press training

When rats reached three mos of age, lever-pressing on the right lever was trained in a manner similar to that described in [36]. The number of sessions required for training ranged between 2 and 5; no group differences were found in the number of sessions required for acquisition of the lever-press.

4.4.2. Fixed ratio schedules

Lever pressing was placed under eight fixed ratio (FR) schedules of reinforcement, in which a fixed number of lever presses resulted in the delivery of a sucrose pellet. Sessions were one hour long, similar to [5]. FR 1 sessions were conducted first. When lever-pressing under FR 1 stabilized (stability was defined as three consecutive sessions in which the number of reinforcers earned did not differ by more than 10% of the mean of those sessions and no trends were apparent), a vehicle (placebo) dose was administered one hour prior to the next FR session. In subsequent sessions, acute doses of rimonabant (1–10 mg kg) were administered one hour prior to the beginning of an experimental session. Each dose of rimonabant was given in increasing half-log units (to reduce the chances of overdose) with at least three days separating doses.

Similar to [5], after the dose–response determination for FR 1 was established, the next schedule, FR 5, was placed in effect until stability ensued and then placebo and rimonabant doses were administered in a manner similar to FR1. This pattern was repeated for subsequent schedules, including FR 15, FR 30, FR 50, FR 90, FR 150, and FR 300. The FR schedules were presented in increasing order to ensure that changes from one FR to the next were constant across rats. Therefore, this procedure was similar to a progressive ratio schedule of reinforcement (see [64,65]), except response requirement changes took place between sessions, rather than within sessions. All procedures were approved by the Idaho State University's Institutional Animal Care and Use Committee.

4.5. Analysis

First, mean number of reinforcers and responses were determined for each group (lean or obese) for each FR under the vehicle, 1 mg/kg, 3 mg/kg, and 10 mg/kg dose of rimonabant. Data were compared between group and FR for each dose of rimonabant (including placebo) by using a two-way ANOVA with repeated measures (group as between-subjects variable and FR as within-subjects variable) for each dose. Partial-eta squared values are reported for effect size; these values refer to the percent of the variance that is attributed to the independent variable. Post-hoc contrasts are reported where appropriate. All 29 rats' data were used for these analyses.

As a secondary analysis, the exponential demand model (Eq. (1)) was fit to each rat's reinforcer data for each dose using non-linear regression. In situations in which 0 reinforcers were earned in a session, 0.1 was substituted, such that log transformation of the data was possible. Values for Q_0 and α were determined and compared across group (obese vs. lean) and drug dose using repeated measures ANOVA.

In addition, the linear-elasticity demand model was used to characterize each rat's reinforcer data. While generally similar to the exponential model in terms of the pattern of behavior that is described, the linear-elasticity equation, in contrast to the exponential model, parses elasticity into three parts:

$$\ln Q = \ln L + b\ln P - aP \tag{2}$$

The free parameters L, b and a describe the curve. L (or the y-intercept of the curve) refers to the projected level of consumption at a very low price (similar to Q_0). The b parameter is the projected slope of the demand curve when there is a small increase from a low price. Usually, this slope is very small, since little change occurs at this point in the curve. The a parameter represents the slope of the demand curve when prices are high enough to affect consumption. From the values of b and a, the point of unit elasticity (p_{max}) was also determined for each rat using Eq. (3):

$$p_{max} = (b+1)/a \tag{3}$$

p_{max} represents the price on a demand curve at which inelastic demand becomes elastic (slope $= -1$) and is used as a measure of elasticity. Response data for each dose were also characterized using Eq. (4):

$$\ln O = \ln L + (b+1)(\ln P) - aP \tag{4}$$

Here, O represents the number of lever presses emitted at each FR value. Each rat's maximal response output (or o_{max}) was determined by finding the solution for Eq. (4) at each rat's p_{max} value.

The mean values of all free parameters, p_{max}, and o_{max} values were compared between groups and across dose using two-way repeated measures analysis.

5. Results

5.1. Vehicle

The top of Fig. 1 shows demand curves from the vehicle condition. As FR increased, the number of sucrose reinforcers earned decreased significantly [$F(1,26) = 182.09$, $p<0.01$, $\eta_p^2 = 0.88$]. The insert, which enhances the scaling from the FR 1–30 values, shows a main effect of genotype — that obese rats earned significantly more sucrose pellets at these values, compared to lean rats [$F(1,26) = 4.1$, $p = 0.05$, $\eta_p^2 = 0.14$], but there were no differences at the higher FR values (50–300). There were no differences between lean and obese rats, in terms of elasticity of demand, when exponential or linear demand analyses were conducted.

The bottom of Fig. 1 shows responses as a function of FR. For both groups, responses increased significantly to a maximal value [o_{max}; $F(3,78) = 109.69$, $p<0.01$, $\eta_p^2 = 0.81$] that corresponded to their p_{max} and declined significantly after that value [$F(3,81) = 29.55$, $p<0.01$, $\eta_p^2 = 0.52$]. The obese rats responded significantly more than leans at FR values 1–30 [$F(1,26) = 3.68$, $p = 0.05$, $\eta_p^2 = 0.13$], but there were no group differences in lean and obese rats at higher FR values.

5.2. Rimonabant

Fig. 2 shows demand curves for all doses of rimonabant for lean and obese rats. For lean rats (top left), rimonabant dose-dependently reduced reinforcers earned [$F(2.74, 263.16) = 45.65$, $p<0.01$, $\eta_p^2 = 0.32$]. There was a main effect of FR [$F(7, 96) = 21.62$, $p<0.01$, $\eta_p^2 = 0.62$] and a dose X FR interaction [$F(19.19, 263.16) = 7.2$, $p<0.01$, $\eta_p^2 = 0.34$]. Contrasts revealed differences between vehicle and 1 mg/kg [$F(1, 96) = 17.67$, $p<0.01$, $\eta_p^2 = 0.16$], 3 mg/kg [$F(1, 96) = 55.35$, $p<0.01$, $\eta_p^2 = 0.37$], and 10 mg/kg doses [$F(1, 92) = 124.73$, $p<0.01$, $\eta_p^2 = 0.57$]. Normalized data, in which all values are expressed as a percent of Q_0, are shown in the bottom left figure for lean rats.

Obese rats (top right) also showed a dose-dependent decrease in reinforcers [$F(2.61, 235.06) = 56.49$, $p<0.01$, $\eta_p^2 = 0.39$], a main effect of FR, [$F(7, 90) = 53.8$, $p<0.01$, $\eta_p^2 = 0.81$], and an interaction [$F(18.28, 235.06) = 6.68$, $p<0.01$, $\eta_p^2 = 0.34$]. Contrasts revealed that vehicle differed significantly from 1 mg/kg [$F(1, 90) = 18.09$, $p<0.01$, $\eta_p^2 = 0.17$], 3 mg/kg [$F(7, 90) = 60.67$, $p<0.01$, $\eta_p^2 = 0.40$], and 10 mg/kg

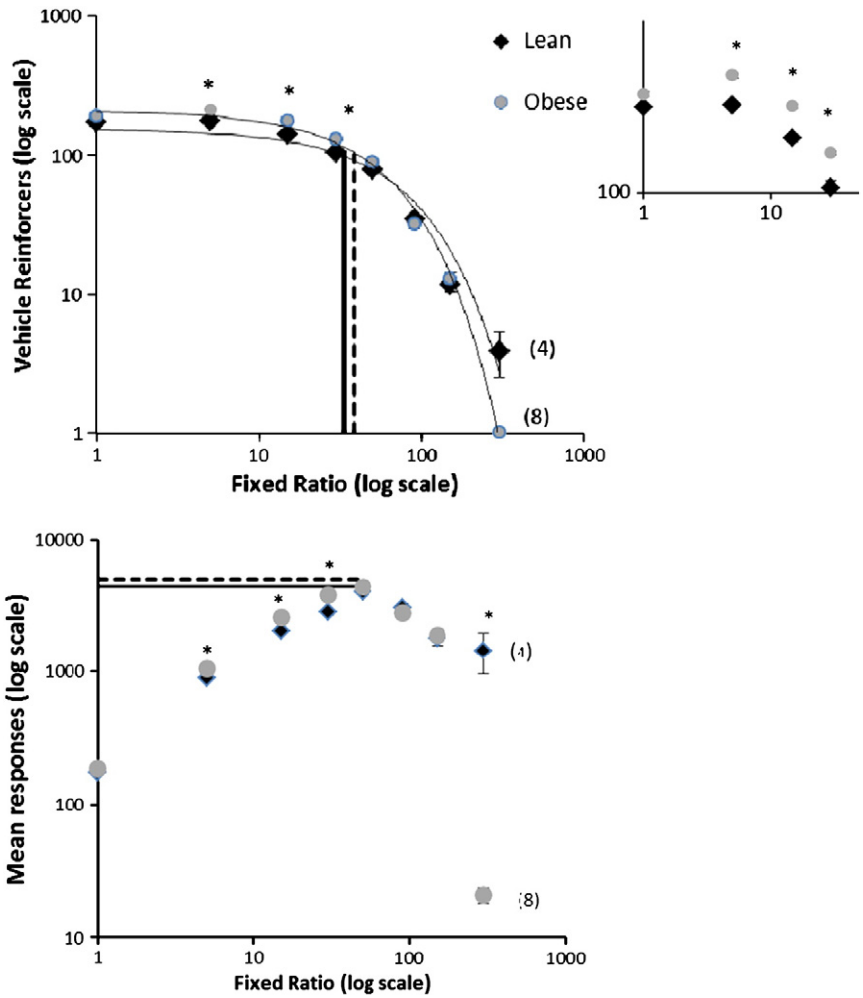

Fig. 1. The number of sucrose reinforcers (top) and responses (bottom) under vehicle earned as a function of fixed ratio. Lean and obese rats are represented as diamonds and circles, respectively. Only four lean and eight obese rats' data were included in the FR 300 condition, as the rest earned 0 responses, and would therefore skew the distributions. P_{max} (top) and o_{max} (bottom) values are represented by vertical and horizontal lines, respectively (lean by solid and obese by dotted). Insert shows a magnified view of reinforcers at fixed ratios of 1–50. Note that data points on all figures obscure the error bars (±1 SEM) in most instances. *$p<0.05$ from post hoc contrasts comparing lean and obese rats.

[$F(1,90)=118.84$, $p<0.01$, $\eta_p^2=0.57$]. Normalized data for obese rats are shown in the bottom right figure.

Fig. 3 shows that across dose, responses showed a biphasic pattern, similar to vehicle data, in which they increased at lower FRs, peaked at a maximal value, and then decreased. This was the case for lean (left) [$F(7,96)=4.87$, $p<0.01$, $\eta_p^2=0.26$] and obese rats (right) [$F(7,78)=17.37$, $p<0.01$, $\eta_p^2=0.57$]. Rimonabant dose-dependently reduced responses for lean [$F(2.28, 15.96)=19.7$, $p<0.01$, $\eta_p^2=0.17$] and obese rats [$F(1.87)=24.24$, $p<0.01$, $\eta_p^2=0.24$]. Contrasts revealed significant reductions at the 1, 3, and 10 mg/kg doses for lean [$F(1, 96)=19.53$, $p<0.01$, $\eta_p^2=0.17$; $F(1, 96)=13.07$, $p<0.01$, $\eta_p^2=0.12$; $F(1,96)=39.93$, $p<0.01$, $\eta_p^2=0.29$, respectively] and obese rats [$F(1, 78)=4.42$, $p=0.04$, $\eta_p^2=0.05$; $F(1, 78)=16.81$, $p<0.01$, $\eta_p^2=0.18$; $F(1, 78)=41.39$, $p<0.01$, $\eta_p^2=0.35$, respectively].

Fig. 4 shows free parameters for the exponential demand equation. Rimonabant dose-dependently increased mean elasticity values (top) [$F(2.38, 64.13)=25.86$, $p<0.01$, $\eta_p^2=0.49$]. Post hoc contrasts showed that the 3 and 10 mg/kg doses significantly differed from vehicle [$F(1, 27)=19.12$, $p<0.01$, $\eta_p^2=0.42$; $F(1, 27)=64.10$, $p<0.01$, $\eta_p^2=0.70$, respectively]. There was a trend toward a group difference, but it was not statistically significant ($p=0.08$, $\eta_p^2=0.11$).

Rimonabant also dose-dependently reduced Q_0 values (bottom) [$F(3, 81)=74.52$, $p<0.01$, $\eta_p^2=0.73$]. Contrasts revealed differences between vehicle and the 3 and 10 mg/kg doses [$F(1,27)=142.29$, $p<0.01$, $\eta_p^2=0.84$; $F(1,27)=174.56$, $p<0.01$, $\eta_p^2=0.87$, respectively]. Again, there was a trend toward a group difference, but it was not significant ($p=0.09$, $\eta_p^2=0.09$).

Table 1 shows free parameters values for the linear demand equation. Rimonabant dose-dependently reduced level of consumption (L) for both lean and obese rats [$F(3,81)=14.71$, $p<0.01$, $\eta_p^2=0.35$] though no group difference or interaction was found. Post hoc contrasts revealed that the 3 and 10 mg/kg doses differed significantly from vehicle [$F(1,27)=10.04$, $p<0.01$, $\eta_p^2=0.27$; $F(1, 27)=63.83$, $p<0.01$, $\eta_p^2=0.71$, respectively]. Rimonabant did not systematically affect the elasticity measures (b or a parameters or p_{max} values).

Fig. 5 shows mean r-squared values for lean and obese rats, as a function of dose for both the linear (solid) and exponential (dashed) models. R-squared values for the exponential model were significantly lower than r-squared values for the linear model [$F(1, 108)=266.84$, $p<0.01$, $\eta_p^2=0.71$]. Obese rats had higher r-squared values than lean rats [$F(1, 108)=3.94$, $p=0.05$, $\eta_p^2=0.04$]. There were no overall effects of rimonabant on r-squared values.

6. Discussion

In the present study, demand for sucrose was examined at FR values between 1 and 300 after administrations of vehicle and various doses of rimonabant. Under vehicle, the number of sucrose pellets decreased as the FR requirement increased for both lean and obese rats; responses increased at lower FR values, then decreased at higher FR

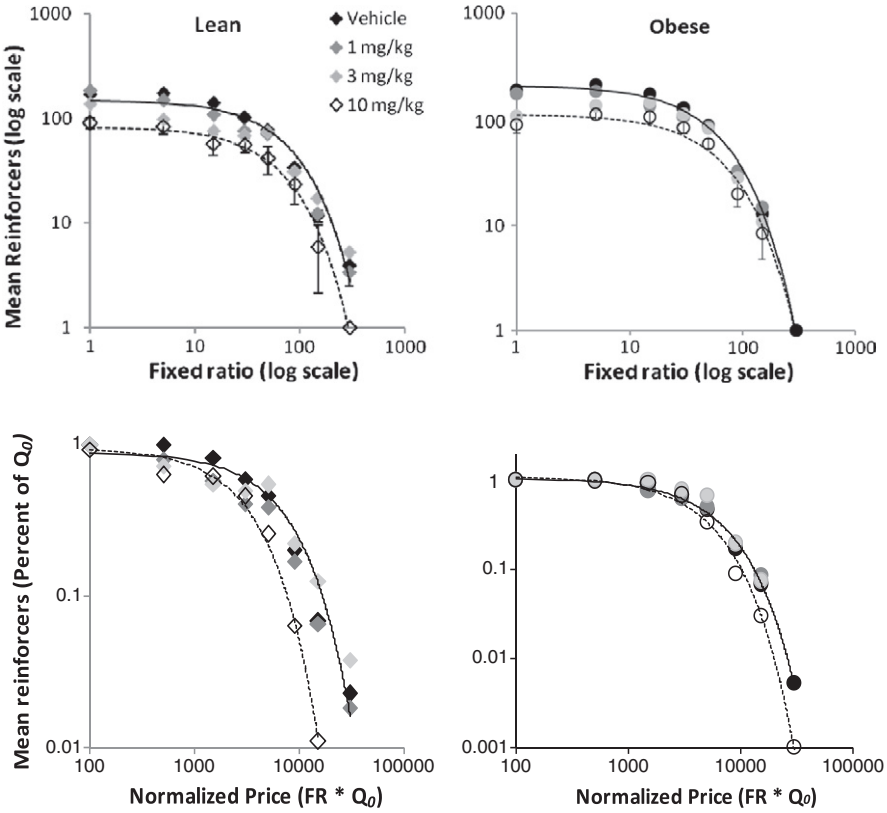

Fig. 2. Demand curves (reinforcers earned as a function of price) for lean (left) and obese (right) Zucker rats for each dose of rimonabant. Normalized curves, in which the number of reinforcers is divided by Q_0, are shown below. All axes are scaled logarithmically. Lines are fit only for the vehicle (solid) and 10 mg/kg dose (dotted) for ease of interpretation.

values. At low FR values (1–30), obese rats earned significantly more sucrose pellets and had significantly higher responses compared to lean rats. At high FR values (50–300), there were no significant differences in responses or sucrose pellet consumption between lean and obese rats. Furthermore, elasticity of demand was not significantly different between lean and obese rats. These results were consistent with the findings by Rasmussen et al. [5], and provide more support for the notion that strain differences for sucrose intake are largest when effort to obtain food is low, but these differences can be overridden by increasing the response requirement to obtain food.

Rimonabant dose-dependently reduced reinforcers earned and responses across all FR values. Rimonabant also increased elasticity of demand for sucrose for both obese and lean rats. These findings are similar to those reported by Rasmussen et al [36], in that rimonabant decreased breakpoints under a progressive ratio (PR) schedule of reinforcement. These results also are consistent with previous research showing that cannabinoid antagonists play a role in reducing food motivation [21,66]. Interestingly, there were no significant strain differences to rimonabant, whereas previous studies have found differences in sensitivity between lean and obese rats to endocannabinoid ligands [62] and antagonists [31,36]. It is unclear why we did not observe significant differences between lean and obese rats in sensitivity to rimonabant, but it is possible that procedural differences were responsible for the disparate results. For instance, in the present study, we used between-session increases in eight different effort conditions (or FRs), whereas previous studies (e.g., [36,63]) used PR schedules for food

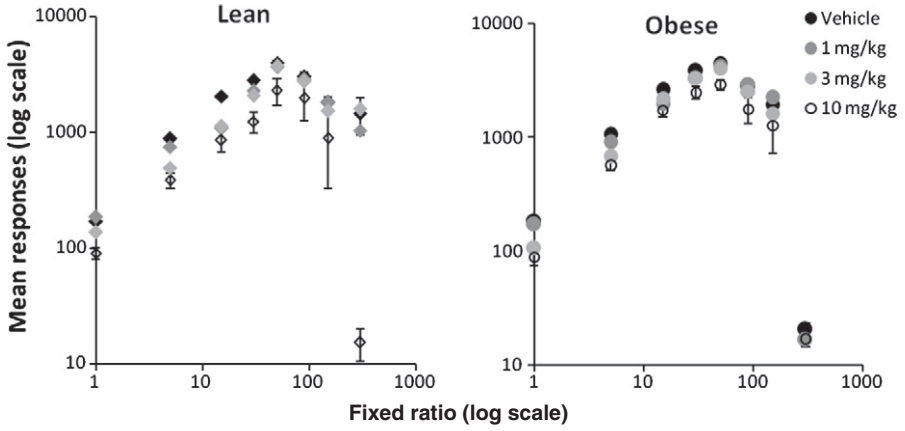

Fig. 3. Mean response output (log scale) as a function of FR for each dose of rimonabant. Lean rats are reresentedon te left and obese on the right. Note that symbols in many cases cover the error bars (±1 SEM).

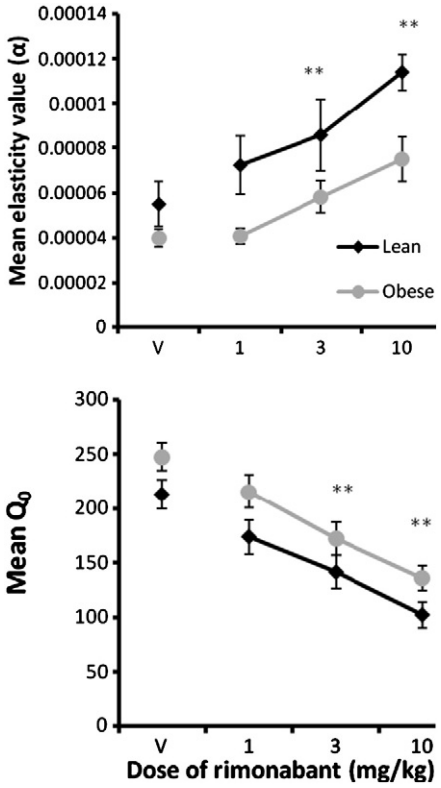

Fig. 4. Free parameters (top = α; bottom = Q_0) of the exponential model of demand as a function of rimonabant dose. Error bars = ±1 SEM. $^{**}p<0.01$ difference compared to vehicle.

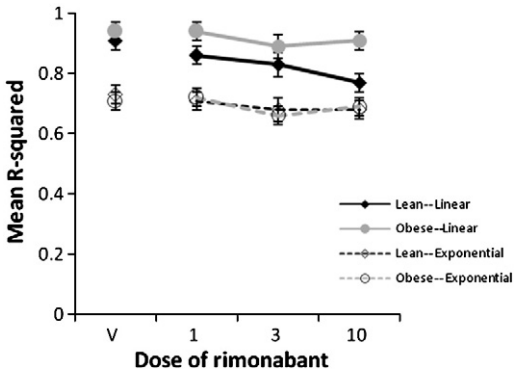

Fig. 5. Compares mean r-squared values between linear (filled) and exponential (open) demand models between lean (diamonds) and obese (circles) rats.

and exercise reward. Testing drug effects on demand functions also requires a greater number of drug administrations – at least one for each of the FR schedules compared to a single dose for one PR schedule – so it is possible that this more prolonged drug testing regimen eliminated differences in sensitivity between the lean and obese rats. More research examining cannabinoid drugs on demand for food is necessary to answer this question.

Both exponential and linear demand functions provided good fits for the data. While the linear model accounted for more variance, which was consistent with Rasmussen et al. [5], the exponential model better described the patterns of the curves in Fig. 2, especially the normalized demand curves. When demand curves are normalized, it is possible to tell whether doses of rimonabant have a similar effect on elasticity. If the normalized curves for each dose overlap completely, then the interpretation is that each dose produces a similar effect on the essential value of food. If the curves do not overlap, e.g., the curves become steeper with increasing dose of rimonabant, the interpretation may be that the drug dose-dependently enhances elasticity, or reduces the essential value of sucrose. This latter interpretation is what the normalized demand curves suggest. In the exponential analysis (Fig. 4), rimonabant dose-dependently increased elasticity values (α), suggesting that the essential value of sucrose indeed is dose-dependently reduced by rimonabant. Moreover, rimonabant dose-dependently reduced Q_0 values, which can also be observed in the non-normalized demand curves of Fig. 2. With the linear model, rimonabant dose-dependently decreased level of consumption (L); however, none of the elasticity measures (b or a parameters or p_{max} values) were affected by rimonabant.

It is unclear why rimonabant did not change any of the linear model's elasticity measures, while it did affect elasticity through the exponential model, though a likely possibility is that there was a large amount of variability in the free parameters of the linear model (Table 1). One contributor to this variability may be the session duration. In typical studies that use demand analysis with food, the session durations are long (typically, between 10 and 24 h; see, e.g., [7,8,11]). These longer sessions allow for large differences in elasticity to be captured between conditions. In shorter sessions, the differences in conditions may be systematic, but may not be enough to generate statistically significant differences in elasticity. For example, in one study [67] hens produced demand curves from sessions that varied between 10, 40, 80, and 120 min. Demand curves from the conditions were orderly from a graphical standpoint — the shorter the session, the more elasticity was observed. However, when comparing elasticity parameters across conditions (b and p_{max} values), there were no significant differences, except in the b values between the 10 and 120 min condition. These data may suggest that the linear model of demand may be more appropriate for examining differences in elasticity in longer sessions. The exponential model, conversely, may be better suited to capture smaller differences in elasticity, such as those generated from shorter sessions. This is useful information for behavioral pharmacological studies, since most acute dose–response information is gleaned from shorter sessions to capture peak drug effects.

Effect sizes, i.e., partial eta-squared values, were reported in this study, which like r-squared values for regression, range from 0 to 1 and specify the percent of variability accounted for by an independent variable. If effect sizes for main effects of rimonabant (range: 0.17 to 0.73; median = 0.35), FR condition (range: from 0.52 to 0.88; median = 0.81), and genetic contributions from lean and obese Zucker rats (range: 0.09 to 0.14; median = 0.12) are considered, FR seems to provide the largest relative influence over sucrose consumption. While it is important to consider these are effect sizes for this particular study only, FR provided the largest relative contribution to food consumption, suggesting that the environmental arrangement of sucrose was most influential to behavior compared to genetic and pharmacological contributions.

Table 1
Mean (SEM) free parameters of the linear demand equation and p_{max} values for lean (top) and obese (bottom) Zucker rats.

	Vehicle	1 mg/kg	3 mg/kg	10 mg/kg
Lean				
L	154.84 (13.54)	148.78 (14.03)	114.09 (13.02)**	75.45 (10.91)**
b	0.059 (0.01)	0.05 (0.009)	0.05 (0.009)	0.05 (0.008)
a	0.37 (0.12)	0.21 (0.11)	0.25 (0.12)	0.26 (0.10)
p_{max}	39.98 (7.41)	36.5 (7.33)	44.84 (11.51)	38.11 (7.75)
Obese				
L	169.73 (16.97)	140.5 (15.98)	121.54 (29.49)**	83.79 (13.45)**
b	0.061 (0.01)	0.05 (0.01)	0.06 (0.01)	0.06 (0.01)
a	0.47 (0.12)	0.45 (0.11)	0.53 (0.15)	0.56 (0.18)
p_{max}	33.1 (3.29)	35.95 (3.51)	33.87 (3.44)	35.29 (3.33)

** $p<0.01$ difference compared to vehicle.

There were some limitations to the present study. First, because an alternate form of food was available outside of experimental sessions, a true closed economy (in which all food is available only within the experimental session) was not arranged. This was done because sucrose pellets do not contain the appropriate nutrition necessary to maintain the health of the animals. Nonetheless, consumption is more inelastic in closed economies, compared to open economies [9,67–69]. Second, and related to the concern of open economy, the present study used 1-h experimental sessions. As mentioned previously, longer sessions, which better approximate closed economies, are associated with more inelastic demand [67]. We used a one-hour duration mainly to capture the peak effect of rimonabant during the sessions. Therefore, it is likely that less elastic demand would be captured with longer session durations and rimonabant may interact with behavior differently in those conditions. A study which characterizes demand using long sessions with closed economies by using drug infusion pumps to maintain a constant drug level (see [70] for discussion on this) would help answer this question.

In addition to attenuating the reinforcing value of food, rimonabant has been associated with an increase in grooming and scratching behavior of Sprague–Dawley rats when measuring activity in an open field [71,72]. Though we did not collect data on those behaviors with the lean or obese Zucker rats from this study, and we did not anecdotally notice any systematic changes in these behaviors, it is possible that grooming or scratching may have competed with bar-pressing, and therefore explains why the number of reinforcers and responses decreased. It is also possible, though, that these behaviors (if they did occur) increased because the rats were pressing the lever fewer times under rimonabant and therefore had more time to engage in other behaviors, such as those that are species-specific.

Finally, it should be noted that rimonabant was dissolved in a solution that comprised a 1:1:18 ratio of ethanol, Cremaphor, and saline. Similar to other studies [21,36,63], the placebo injections contained only saline. Therefore it is possible that the very small amount of ethanol and Cremaphor may have contributed to the rimonabant-related effects observed in the data. It is unlikely, however, because the levels were far below what is behaviorally active.

7. Conclusions

Despite these limitations, the data suggest that rimonabant-related effects on elasticity were captured in hour-long sessions. The results from the present study, then, provide further support that the endocannabinoid system is important in motivation for sucrose-based (or sweet) foods, and provide further evidence that cannabinoid antagonists can be used to alter the reinforcing efficacy, i.e., essential value, of sucrose reward. This study, to our knowledge, was the first to use a demand analysis to evaluate drug effects on sucrose reward. A demand analysis provides more information about the reinforcing efficacy of food compared to the more traditional free-food intake studies, as it examines stable behavior under a range of response requirements. In the natural environment, effort required to obtain food varies. Therefore, understanding how effort required to obtain food interacts with genetic contributors and pharmacological alterations to food motivation may be important to consider when developing potential treatments of obesity [70].

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References

[1] Bickel WK, Vuchinich RE. Reframing health: behavioral change with behavioral economics. Mahwah, NJ: Lawrence Erlbaum Associates; 2000.
[2] Heather N, Vuchinich RE. Choice, behavioural economics and addiction, vol. 1. Kidlington, UK: Elsevier Ltd; 2003.
[3] Epstein LH, Leddy JJ, Temple JL, Faith MS. Food reinforcement and eating: a multilevel analysis. Psychol Bull 2007;133(5):884–906.
[4] Epstein LH, Saelens BE. Behavioral economics of obesity: food intake and energy expenditure. In: Bickel WK, Vuchinich RE, editors. Reframing health: behavioral change with behavioral economics. Mahwah, NJ: Lawrence Erlbaum Associates; 2000. p. 293–311.
[5] Rasmussen EB, Reilly W, Hillman C. Demand for sucrose in lean and obese Zuckers. Behav Processes 2010;85(2):191–7.
[6] Atalayer D, Rowland N. Meal patterns of mice under systematically varying approach and unit costs for food in a closed economy. Physiol Behav 2009;98:85–93.
[7] Madden GJ, Smethells JR, Ewan EE, Hursh SR. Tests of behavioral-economic assessments of relative reinforcer efficacy II: economic complements. J Exp Anal Behav 2007;88(3):355–67.
[8] Hursh SR. Economic concepts for the analysis of behavior. J Exp Anal Behav 1980;34:219–38.
[9] Hursh SR. Behavioral economics. J Exp Anal Behav 1984;42:435–52.
[10] Hursh SR. Behavioral economic concepts and methods for studying health behavior. In: Bickel WK, Vuchinich RE, editors. Reframing health: behavioral change with behavioral economics. Mahwah, NJ: Lawrence Erlbaum Associates; 2000. p. 27–60.
[11] Hursh SR, Raslear TG, Shurtleff D, Bauman R, Simmons L. A cost-benefit analysis of demand for food. J Exp Anal Behav 1988;50(3):419–40.
[12] Duran C, McSweeney FK. Rate of responding as a function of ratio requirement when no supplemental feedings are given. Behav Processes 1987;15(2–3):293–303.
[13] Hursh SR, Silberberg A. Economic demand and essential value. Psychol Rev 2008;115(1):186–98.
[14] Drewnowski A, Grinker JA. Temporal effects of delta-9-tetrahydrocannabinol on feeding patterns and activity of obese and lean Zucker rats. Behav Biol 1978;23(1):112–7.
[15] Williams C, Rogers P, Kirkham T. Hyperphagia in pre-fed rats following ordal delta-9 THC. Physiol Behav 1998;65:343–6.
[16] Williams C, Kirkham T. Anandamide induces overeating: mediation by central cannabinoid receptors. Psychopharmacology (Berl) 1999;143(3):315–7.
[17] Hao S, Avraham Y, Mechoulam R, Berry EM. Low dose anandamide affects food intake, cognitive function, neurotransmitter and corticosterone levels in diet restricted mice. Eur J Pharmacol 2000;392:147–56.
[18] DiMarzo V, Goparaju SKI, Wang L, Liu J, Batkai S, Jarai Z, et al. Leptin regulated endocannabinoids are involved in maintaining food intake. Nature 2001;410:822–5.
[19] Kirkham T, Williams C. Endogenous cannabinoids and appetite. Nutr Res Rev 2001;14:65–86.
[20] Berry E, Mechoulam R. Tetrahydrocannabinol and endocannabinoids in feeding and appetite. Pharmacol Ther 2002;95(2):185–90.
[21] Wakley AA, Rasmussen EB. Effects of cannabinoid drugs on the reinforcing properties of food in gestationally undernourished rats. Pharmacol Biochem Behav 2009;94:30–6.
[22] Gomez R, Navarro M, Ferrer B, Trigo JM, Bilbao A, Del Arco I, et al. A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. J Neurosci 2002;22(21):9612–7.
[23] Bergman J, Delatte MS, Paronis CA, Vemuri K, Thakur GA, Makriyannis A. Some effects of CB1 antagonists with inverse agonist and neutral biochemical properties. Physiol Behav 2008;93(4–5):666–70.
[24] Bermudez-Silva F, Viveros MP, McPartland JM, Rodriguez de Fonseca F. The endocannabinoid system, eating behavior, and energy homeostasis: the end or a new beginning? Pharmacol Biochem Behav 2010;95(4):375–82.
[25] Droste SM, Saland SK, Schlitter EK, Rodefer JS. AM 251 differentially effects food-maintained responding depending on food palatability. Pharmacol Biochem Behav 2010;95(4):443–8.
[26] André A, Gonthier M. The endocannabinoid system: its roles in energy balance and potential as a target for obesity treatment. Int J Biochem Cell Biol 2010;42(11):1788–801.
[27] Bellocchio LC, Pasquali R, Pagotto U. The endocannabinoid system and energy metabolism. J Neuroendocrinol 2008;20(6):850–7.
[28] Colombo G, Agabio R, Diaz G, Lobina C, Reall R, Gessa GL. Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. Life Sci 1998;63(8):PL113–7.
[29] Simiand J, Keane M, Keane PE, Soubrié P. SR141716, a CB1 cannabinoid antagonist, selectively reduces sweet food intake in the marmoset. Behav Pharmacol 1998;9(2):179–81.
[30] McLaughlin PJ, Winston K, Swezey L, Wisniecki A, Aberman J, Tardif DJ, et al. The cannabinoid CB1 antagonists SR 141716A and AM 251 suppress food intake and food-reinforced behavior in a variety of tasks in rats. Behav Pharmacol 2003;14(8):583–8.
[31] Vickers SP, Webster LJ, Wyatt A, Dourish CT, Kennett GA. Preferential effects of the cannabinoid CB1 receptor antagonist, SR 141716, on food intake and body weight gain of obese (fa/fa) compared to lean Zucker rats. Psychopharmacology (Berl) 2003;167(1):103–11.
[32] Thornton-Jones ZD, Vickers SP, Clifton PG. The cannabinoid CB1 receptor antagonist SR141716A reduces appetitive and consummatory responses for food. Psychopharmacology (Berl) 2005;179(2):452–60.

[33] Carai MA, Colombo G, Maccioni P, Gessa GL. Efficacy of rimonabant and other cannabinoid CB1 receptor antagonists in reducing food intake and body weight: preclinical and clinical data. CNS Drug Rev 2006;12(2):91–9.
[34] Gardner A, Mallet PE. Suppression of feeding, drinking, and locomotion by a putative cannabinoid receptor 'silent antagonist'. Eur J Pharmacol 2006;530(1–2):103–6.
[35] Herling AW, Kilp S, Elvert R, Haschke G, Kramer W. Increased energy expenditure contributes more to the body weight reducing effect of rimonabant than reduced food intake in candy-fed Wistar rats. Endocrinology 2008;149(5):2557–66.
[36] 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.
[37] Serrano A, Del Arco I, Javier Pavon F, Macias M, Perez-Valero V, Rodriguez de Fonseca F. The cannabinoid CB1 receptor antagonist SR141716A (Rimonabant) enhances the metabolic benefits of long-term treatment with oleoylethanolamide in Zucker rats. Neuropharmacology 2008;54(1):226–34.
[38] Banerji MA, Tiewala M. Rimonabant—the RIO North America trial: a new strategy to sustaining weight loss and related morbidity. Curr Diab Rep 2006;6(3):228–9.
[39] Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 2006;295(7):761–75.
[40] Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006;368(9548):1660–72.
[41] Despres JP, Golay A, Sjostrom L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005;353(20):2121–34.
[42] Scheen AJ. CB1 Receptor blockade and its impact on cardiometabolic risk factors: overview of the RIO programme with rimonabant. J Neuroendocrinol 2008;20:139–46.
[43] Van Gaal L, Pi-Sunyer X, Despres JP, McCarthy C, Scheen A. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. Diabetes Care 2008;31:S229–40.
[44] Administration, U.F.a.D. Testimony before FDA Advisory Committee of rimonabant. HRG Publication, 1815; 2007.
[45] Le Foll B, Gorelick DA, Goldberg SA. The future of endocannabinoid-oriented clinical research after CB1 antagonists. Psychopharmacology (Berl) 2009;205(1):171–4.
[46] DiPatrizio NV, Simansky KJ. Activating parabrachial cannabinoid CB1 receptors selectively stimulates feeding of palatable foods in rats. J Neurosci 2008;28:9702–9.
[47] Beardsley PM, Thomas BF, McMahon LR. Cannabinoid CB1 receptor antagonists as potential pharmacotherapies for drug abuse disorders. Int Rev Psychiatry 2009;21(2):134–42.
[48] Pagotto U, Vicennati V, Pasquali R. The endocannabinoid system and the treatment of obesity. Ann Med 2005;37(4):270–5.
[49] Drewnowski A, Grinker JA. Food and water intake, meal patterns and activity of obese and lean Zucker rats following chronic and acute treatment with delta-9-tetrahydrocannabinol. Pharmacol Biochem Behav 1978;9(5):619–30.
[50] Yoshimatsu H, Machidori H, Doi T, Kurokawa M, Ookuma K, Kang M, et al. Abnormalities in obese Zuckers: defective control of histaminergic functions. Physiol Behav 1993;54(3):487–91.
[51] DiPatrizio NV, Astarita G, Schwartz G, Xiaosong L, Piomelli D. Endocannabinoid signal in the gut controls dietary fat intake. Proc Natl Acad Sci U S A 2011;108(31):12904–8.
[52] Mahler SV, Smith KS, Berridge KC. Endocannabinoid hedonic hotspot for sensory pleasure: Anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward. Neuropsychopharmacology 2007;32:2267–78.
[53] Wade-Galuska T, Galuska C, Winger G. Effects of daily morphine administration and deprivation on choice and demand for remifentanil and cocaine in rhesus monkey. J Exp Anal Behav 2011;95:75–89.
[54] Christensen CJ, Kohut SJ, Handler S, Silberberg A, Riley AL. Demand for food and cocaine in Fischer and Lewis rats. Behav Neurosci 2009;123(1):165–71.
[55] Christensen CJ, Silberberg A, Hursh SR, Roma PG, Riley AL. Demand for cocaine and food over time. Pharmacol Biochem Behav 2008;91(2):209–16.
[56] Kurtz TW, Morris RC, Pershadsingh HA. The Zucker fatty rat as a genetic model of obesity and hypertension. Hypertension 1989;13(6 Pt 2):896–901.
[57] Siddiqui AH, Ali Q, Hussain T. Protective role of angiotensin II subtype 2 receptor in blood pressure increase in obese Zucker rats. Hypertension 2009;53(2):256–61.
[58] Inokuchi J. Insulin resistance as a membrane microdomain disorder. Biol Pharm Bull 2006;29(8):1532–7.
[59] Beck B. Neuropeptides and obesity. Nutrition 2000;16(10):916–23.
[60] Sahu A. Minireview: a hypothalamic role in energy balance with special emphasis on leptin. Endocrinology 2004;145:2613–20.
[61] Thanos PK, Ramalhete RC, Michaelides M, Piyis YK, Wang GJ, Volkow ND. Leptin receptor deficiency is associated with upregulation of cannabinoid 1 receptors in limbic brain regions. Synapse 2008;62(9):637–42.
[62] Smith S, Rasmussen EB. Effects of 2-AG on the reinforcing properties of wheel activity in obese and lean Zucker rats. Behav Pharmacol 2010;21:292–300.
[63] Rasmussen EB, Hillman C. Rimonabant and naloxone reduce the reinforcing properties of exercise. Exp Clin Psychopharmacol 2011; in press.
[64] Hodos W. Progressive ratio as a measure of reward strengh. Science 1961;269:943–4.
[65] Stafford D, LeSage MG, Glowa JR. Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: a review. Psychopharmacology (Berl) 1998;139(3):169–84.
[66] Maccioni P, Pes D, Carai MA, Gessa GL, Colombo G. Suppression by the cannabinoid CB1 receptor antagonist, rimonabant, of the reinforcing and motivational properties of a chocolate-flavoured beverage in rats. Behav Pharmacol 2008;19(3):197–209.
[67] Foster TM, Kinloch J, Poling A. The effects of session length on demand functions generated using FR schedules. J Exp Anal Behav 2011;95:289–304 [68].
[68] Houston A, McNamara J. The value of food: effects of open and closed economies. Anim Behav 1989;37:546–62.
[69] Collier G, Johnson DF, Morgan C. The magnitude-of-reinforcement function in closed and open economies. J Exp Anal Behav 1992;57(1):81–9.
[70] Rowland NE, Vaughan CH, Mathes CM, Mitra A. Feeding behavior, obesity, and neuroeconomics. Physiol Behav 2008;93(1–2):97–109.
[71] Järbe TU, Andrzejewski ME, DiPatrizio NV. Interactions between the CB1 receptor agonist Delta 9-THC and the CB1 receptor antagonist SR-141716 in rats: open-field revisited. Pharmacol Biochem Behav Nov 2002;73(4):911–9.
[72] Järbe TU, DiPatrizio NV, Li C, Makriyannis A. The cannabinoid receptor antagonist SR-141716 does not readily antagonize open-field effects induced by the cannabinoid receptor agonist (R)-methanandamide in rats. Pharmacol Biochem Behav Jul 2003;75(4):809–21.