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A Behavioral and Pharmacological Characterization of Palatable Diet Alternation in Mice

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Abstract

Obesity and eating disorders are widespread in Western societies. Both the increased availability of highly palatable foods and dieting are major risk factors contributing to the epidemic of disorders of feeding. The purpose of this study was to characterize an animal model of maladaptive feeding induced by intermittent access to a palatable diet alternation in mice. In this study, mice were either continuously provided with standard chow food (*Chow/Chow*), or provided with standard chow for 2 days and a high-sucrose, palatable food for 1 day (*Chow/Palatable*). Following stability of intake within the cycling paradigm, we then investigated the effects of several pharmacological treatments on excessive eating of palatable food: naltrexone, an opioid receptor antagonist, SR141716A, a cannabinoid-1 receptor antagonist/inverse agonist, and BD-1063, a sigma-1 receptor antagonist. Over successive cycles, *Chow/Palatable* mice showed an escalation of palatable food intake within the first hour of renewed access to palatable diet and displayed hypophagia upon its removal. Naltrexone, SR141716A, and BD-1063 all reduced overconsumption of palatable food during this first hour. Here we provide evidence of strong face and convergent validity in a palatable diet alternation model in mice, confirming multiple shared underlying mechanisms of pathological eating across species, and thus making it a useful therapeutic development tool.

Keywords

Food intake; overeating; palatable diet; naltrexone; SR141716A; BD-1063

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Conflict of interest

None.

1. Introduction

Maladaptive eating behavior is commonly observed in some forms of obesity and certain eating disorders, such as binge eating disorder (BED) as well as the recently proposed food addiction (American Psychiatric Association, 2013; Davis, 2013; de Zwaan, 2001; Gearhardt et al., 2009; Moore et al., 2017c; Schulte et al., 2015). A hypothesized major contributor to the rise in obesity and eating disorders is the high reinforcing efficacy of palatable food (i.e. food rich in sugars and/or fats), which is responsible for an increase in consumption (Avena and Gold, 2011; Berthoud, 2012; Gearhardt et al., 2011; Moore et al., 2017b; Morris et al., 2015). Furthermore, individuals will often resort to dieting or limiting dietary intake to low-calorie, “safe” foods, which are broadly less palatable than high-calorie foods, and abstain from “forbidden” food of high-calorie content and high palatability (Hofmann et al., 2014; Mela, 2001). Ultimately, those who diet or abstain from palatable food will return to foods of high palatability (Pankevich et al., 2010). As a result, a history of dieting features repeated, discrete alternations in intake of “safe” food with highly palatable foods, rich in fat and/or sugar (Laessle et al., 1989; Mela, 2001; Polivy and Herman, 1985). Thus, a history of dieting is recognized as a major risk factor for developing obesity as well as eating disorders (Dulloo and Montani, 2015; Lowe et al., 2013).

Our laboratory has previously employed an experimental paradigm to mimic both overconsumption and dieting, through alternating access to a highly palatable diet in rats (Blasio et al., 2014a; Dore et al., 2014). In this model, across 3-day cycles, animals receive alternating access to a control chow diet (2 days) and a high-sucrose, highly palatable diet (1 day) (Blasio et al., 2014a; Dore et al., 2014). This and other models of palatable diet cycling in rats have led to several advances in the understanding of the psychobehavioural and neuropharmacological mechanisms of disordered eating. However, in mice, the validation of behavioral models of diet alternation is less developed. Once characterized, clinically relevant behavioral paradigms can be combined with the numerous and easily accessible genetic technologies available for mice (i.e. knockout/knockin models, Cre-recombinase lines, transgenic lines). Thus, the first aim of this study was to test the face validity of a model of intermittent cycling access of palatable food in mice.

Multiple neurotransmitter systems have been identified as pharmacotherapeutic targets for obesity and disordered eating, including opioid, cannabinoid-1 (CB1), and sigma-1 (Sig-1) receptor systems. In rat models of disordered eating, antagonism of the above receptors is able to reduce palatable food overconsumption (Blasio et al., 2014b; Cottone et al., 2012; Dore et al., 2014). Thus, a secondary aim of this study was to evaluate the convergent validity of the diet alternation model in mice by evaluating the effects of pretreatment with naltrexone, an opioid receptor antagonist, SR141716A, a CB1 receptor antagonist/inverse agonist, and BD-1063, a Sig-1 receptor antagonist on palatable food intake.

2. Materials and Methods

2.1 Subjects

Male C57Bl/6J mice ($N=73$), (7 weeks old upon arrival, Jackson Laboratory) weighing 22–29 g, were single housed in wire-topped, plastic cages (16.76 cm × 27.94 cm × 12.32 cm)

on a 12-hour reverse light cycle (lights off at 10:00 a.m.), in an AAALAC-approved humidity-(60%) and temperate-controlled (22°C) vivarium. Mice had access to food and water *ad libitum* at all times unless otherwise stated. All experimental protocols used in this study adhered to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Principles of Laboratory Animal Care, and were approved by the Boston University Medical Campus Institutional Animal Care and Use Committee.

2.2 Food

Corn-based chow (Teklad Global Diet 2918 (44.2% carbohydrate, 6.2% fat, 18.6% protein, metabolizable energy 3.1 cal/g; Harlan, Indianapolis, IN) was used as the control diet. A highly palatable and nutritionally complete, chocolate-flavored, high-sucrose, AIN-76A-based diet, comparable in macronutrients and energy density to the chow diet (Formula 5TUL: 66.7% carbohydrate, 12.7% fat, 20.6% protein, metabolizable energy 3.44 cal/g; TestDiet, Richmond, IN), was used as the experimental diet.

2.3 Palatable Diet Cycling

An intermittent palatable diet access paradigm was used, similar to the one previously described in rats (Blasio et al., 2014a; Dore et al., 2014). After arrival and one-week acclimation period, mice were divided into two experimental diet groups matched for food intake, body weight, and feed efficiency from a 4-day baseline period. One diet group then had *ad libitum* access to the chow diet ('Chow') (*Chow/Chow*) at all times, while the other diet group had *ad libitum* access to the chow diet for 2 days, followed by a single day of *ad libitum* access to the more palatable, chocolate-flavored, high-sucrose diet ('Palatable'; *Chow/Palatable*; $N=16$). The *Chow/Chow* diet group ($N=9$) served as a control for all comparisons and analysis against the experimental *Chow/Palatable* diet group. For simplicity, the first 2 days (chow diet only) and the following 1 day (chow or palatable diet according to diet group) are referenced in all experiments as *C* and *P Phase*, respectively. Thus, a 3-day period was defined as a diet 'cycle'. Diets were never simultaneously available in any single cage. Diet switch occurred before lights turned off at 10:00 a.m. Food intake and body weight were measured at the onset of each successive phase, when the *Chow/Palatable* diet group was switched from one diet to the other. An additional food intake measurement took place for both diet groups 1-hour following the onset of each *P Phase*, to serve as an evaluation of the escalation of palatable diet consumption across consecutive cycles (Blasio et al., 2014a; Dore et al., 2014). Average food intake was determined by kilocalories (kcal) consumed in a particular phase divided by the number of days in that phase (2 for *C Phase*, 1 for *P Phase*). Similarly, average body weight change was computed as the difference between the body weight at the end and at the beginning of that phase divided by the number of days in that phase. Feed efficiency was determined by body weight (mg) gained in a given time divided by the food intake (kcal) within that same time. Cumulative food intake and cumulative body weight gain were determined as the difference between the food consumed (kcal) or the body weight gained between the end of a complete cycle and the beginning of the study (g).

2.4 Drugs

The opioid receptor antagonist naltrexone [(5a)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride] was solubilized immediately prior to treatment in isotonic filtered saline (0.9%) (Cole et al., 2000) and administered intraperitoneally (0, 1 mg/kg, 10 mg/kg, 30 min pretreatment). Chosen doses and pretreatment time were based on previous literature (Escher and Mittleman, 2006; Moslehi et al., 2014; Stafford et al., 2015).

The CB1 receptor antagonist/inverse agonist SR141716A [rimonabant or 5-(4-Chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide hydrochloride] was solubilized immediately prior to treatment in an 18:1:1 mixture of saline:ethanol:cremophor as determined previously (Dore et al., 2014), and administered intraperitoneally (0, 3 mg/kg, 10 mg/kg, 30 min pretreatment). Chosen doses and pretreatment time were based on previous literature (Dol-Gleizes et al., 2009; Duarte et al., 2004; Ward et al., 2007; Wiley et al., 2005).

The Sig-1 receptor antagonist BD-1063 $\times$ 2HBr salt (1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine dyhydrobromide) was solubilized immediately prior to treatment in isotonic filtered saline (0.9%) (Kotagale et al., 2013) and administered intraperitoneally (0, 10 mg/kg, 30 mg/kg, 15 min pretreatment). Chosen doses and pretreatment time were based on previous literature (Brammer et al., 2006; Liu et al., 2005; Liu and Matsumoto, 2008; Nguyen et al., 2014).

2.5 Pharmacological Treatment Effects on Excessive Eating of Palatable Food

In a separate group of mice with a history of intermittent palatable diet access paradigm, Naltrexone, SR141716A, and BD-1063 were administered in within-subject Latin square designs (N=24 per group). After stable first hour food intake was established, drug treatments occurred a minimum of 3 days apart for doses of the same drug, and a minimum 5 days apart between different drugs. Following drug administration and a pretreatment period where food was withheld, mice were given access to a pre-weighed amount of either chow or palatable diet. Food intake was measured again 1-hour later. Body weights were recorded at time of drug administration and 24 hours later to evaluate drug effects on body weight.

2.6 Statistical Analyses

Average daily food intake (kcal), average daily body weight change (g), and average daily feed efficiency (g/kcal) across 10 cycles were examined by means of 3-way mixed analysis of variance (ANOVAs) with Diet Group (*Chow/Chow*, or *Chow/Palatable*) as a between-subjects factor, and Phase (*P Phase*, or *C Phase*) and Cycle (1 to 10 cycles) as within-subject factors. First hour of palatable food consumption (escalation 1hr (kcal)), cumulative food intake (kcal), cumulative body weight change (g), and cumulative feed efficiency (g/kcal) were examined by means of 2-way ANOVAs with Diet Group as a between-subjects factor and Cycle as a within-subject factor. Sigmoidal four-parameter logistic regression function was fit to 1 hr palatable food intake (kcal) (Hartz et al., 2001). Pharmacological treatment effects on food intake (kcal) and body weight change (g) were analyzed with 2-way ANOVAs with Diet Group as a between-subjects factor and Dose as a within-subject factor.

Group comparisons used Student's *t*-tests (2-group comparisons) or analysis of variance (ANOVA) (3-group comparisons), the latter interpreted by simple main effect analysis or Newman-Keuls comparisons after significant omnibus effects ($p < 0.05$). The software/graphic packages used were SigmaPlot 11.0 (Systat Software Inc., Chicago, IL) and Statistica 7.0 (Statsoft, Inc., Tulsa, OK).

3. Results

3.1 Effects of the Intermittent Access Cycling Model on Food Intake and Body Weight

Alternating access to the high-sucrose, palatable diet led to progressive changes in food intake of mice in a diet-specific manner between the *C Phase* and *P Phase* [Cycle $\times$ Diet Phase $\times$ Diet Group: $F(9,207) = 3.55$, $p < 0.001$]. No difference in standard chow intake was observed between groups during the first *C Phase*, a time point at which *Chow/Palatable* mice had not been exposed to the palatable diet yet. As shown in Figure 1A, hyperphagia already emerged during the first access to the highly palatable diet (*P Phase*) and continued throughout the 10 cycles of observations in the *Chow/Palatable* diet group, as compared to control *Chow/Chow* mice (Figure 1A). Conversely, when access to the standard chow diet was renewed, following access to the palatable diet, the *Chow/Palatable* group showed hypophagia, as compared to controls, throughout the entire period of observation. Over the course of 10 successive cycles, *Chow/Palatable* mice cumulatively ate a greater amount of food compared to *Chow/Chow* mice (kcal) [Diet Group: $F(1,23) = 233.48$, $p < 0.001$; Figure 1B]. This effect was due to a proportionally greater eating of highly palatable food during the *P Phase* [$M \pm \text{SEM}$: 148.15 ± 2.71 greater kcal, +36% vs. *Chow/Chow* mice, sum of *P Phase* intakes across 10 cycles] compared to the underconsumption during chow hypophagia [$M \pm \text{SEM}$: 77.71 ± 2.19 lower kcal, -26% vs. *Chow/Chow* mice, sum of *C Phase* intakes across 10 cycles]. *Chow/Palatable* mice cumulatively ingested more food than *Chow/Chow* controls [Cycle: $F(9,207) = 4529.83$, $p < 0.001$; Cycle $\times$ Diet Group: $F(9,207) = 132.91$, $p < 0.001$] starting from the second cycle and until the end of the observation period.

Mirroring food intake, daily body weight change of *Chow/Palatable* mice fluctuated across the 10 successive cycles in a phase- and diet-specific manner [Cycle $\times$ Diet Phase $\times$ Diet Group: $F(9,207) = 3.68$, $p < 0.001$; Figure 1C]. *Chow/Palatable* mice showed greater body weight gain compared to *Chow/Chow* controls during the *P Phase* [$M \pm \text{SEM}$ of average *P Phase* body weight gain: 1.22 ± 0.05 g vs. 0.13 ± 0.04 g; $t(23) = -14.45$, $p < 0.001$; *Chow/Chow* and *Chow/Palatable* mice, respectively, Figure 1C], beginning after only one cycle ($p < 0.001$). Subsequently, during the *C Phase*, *Chow/Palatable* mice showed an absolute loss of body weight [$M \pm \text{SEM}$ of average *C Phase* body weight gain: -0.47 ± 0.03 g vs. 0.06 ± 0.02 g; $t(23) = 13.10$, $p < 0.001$; *Chow/Chow* and *Chow/Palatable* mice, respectively, Figure 1C]. Cumulative body weight gain (g) across 10 cycles demonstrated differences between diet groups [Diet Group: $F(1,23) = 6.96$, $p < 0.05$; Figure 1D], across cycles [Cycle: $F(9,207) = 29.76$, $p < 0.001$], and an interaction of cycle and diet group [Cycle $\times$ Diet Group: $F(9,207) = 2.95$, $p < 0.05$]. Following the first cycle containing palatable food access, *Chow/Palatable* mice exhibited higher body weight gain, which slowly increased over time. Conversely, *Chow/Chow* mice steadily gained weight, to the end that groups became similar after 6 cycles.

Feed efficiency (g/kcal) also fluctuated across cycles in a phase- and diet-specific manner [Cycle $\times$ Phase $\times$ Diet Group: $F(9,207) = 3.55$, $p < 0.001$; Figure 1E]. Cumulative feed efficiency (g/kcal) across 10 successive cycles was not different between diet groups [Diet Group: $F(1,23) = 0.23$, *n.s.*], though it did increase across cycles in a diet-specific manner [Cycle: $F(9,207) = 28.85$, $p < 0.001$; Cycle $\times$ Diet Group: $F(9,207) = 5.29$, $p < 0.001$; Figure 1F]. Similarly to cumulative body weight gain, cumulative feed efficiency differed between groups, as *Chow/Palatable* mice exhibited greater efficiency immediately following palatable diet access, and *Chow/Chow* mice exhibited steady feed efficiencies over time.

3.2 Effects of Diet Alternation on Escalation of Palatable Food Consumption in Chow/Palatable Mice

Chow/Palatable mice escalated their food intake during the first hour of renewed access over 10 successive cycles [Cycle $\times$ Diet Group: $F(9,207) = 7.78$, $p < 0.001$; Figure 2]. From the first introduction of the palatable diet *Chow/Palatable* mice consumed more food than *Chow/Chow* mice in the first hour of access [$t(23) = -2.72$, $p < 0.05$], and by the ninth cycle their intake was approximately five-fold that of *Chow/Chow* mice [$t(23) = -9.88$, $p < 0.001$], which represented $18.6\% \pm 1.1$ of the *P Phase* daily intake of *Chow/Palatable* mice vs. $5.5\% \pm 1.3$ of the daily intake of *Chow/Chow* mice. The escalation was experience-dependent, supported by a strong fit with the sigmoidal associative learning function ($M \pm \text{SEM}$, min: 0.07 ± 4.5 , max: 2.90 ± 1.1 , ET50: 1.68 ± 3.6 , Hillslope: 1.31 ± 2.59 , $r = 0.93$, $p < 0.01$).

3.3 Effects of Naltrexone on Food Intake and Body Weight Gain

Pretreatment with naltrexone significantly reduced palatable food intake in *Chow/Palatable* mice within the first hour [Dose $\times$ Diet Group: $F(2,44) = 10.98$, $p < 0.001$; Figure 3A]. The reduction in palatable food intake by naltrexone was dose-dependent; as the 10 mg/kg dose further reduced intake compared to the 1 mg/kg dose. Naltrexone did not affect standard chow intake in *Chow/Chow* mice.

In addition, drug treatment did not affect body weight change [Dose: $F(2,44) = n.s.$; Dose $\times$ Diet Group: $F(2,44) = n.s.$; Figure 3B]. Naltrexone therefore selectively decreased palatable food consumption in *Chow/Palatable* mice, without affecting body weight gain.

3.4 Effects of SR141716A on Food Intake and Body Weight Gain

Pretreatment with SR141716A significantly reduced palatable food intake in *Chow/Palatable* mice within the first hour [Diet Group $\times$ Dose: $F(2,44) = 11.66$, $p < 0.001$; Figure 3B]. Furthermore, *Chow/Palatable* mice treated with the 3 mg/kg and 10 mg/kg dose consumed an equal amount of food as *Chow/Chow* mice under vehicle conditions, indicating a complete blockade of excessive eating. Both doses of SR141716A reduced palatable food intake equally effectively in *Chow/Palatable* mice. SR141716A treatment did not affect chow intake in *Chow/Chow* mice.

SR141716A dose-dependently decreased body weight gain [Dose: $F(2,44) = 102.85$, $p < 0.001$; Figure 3E], though similarly in both diet groups [Dose $\times$ Diet Group: $F(2,44) = 2.46$, *n.s.*].

3.5 Effects of BD-1063 on Food Intake and Body Weight Gain

Pretreatment with BD-1063 significantly reduced palatable food intake in *Chow/Palatable* mice during the first hour of access [Dose $\times$ Diet Group: $F(2,44) = 18.41$, $p < 0.001$; Figure 3C]. While pretreatment of 10 mg/kg BD-1063 did not significantly reduce palatable food intake, pretreatment with 30 mg/kg resulted in a significant reduction in intake compared to vehicle conditions ($p < 0.001$). BD-1063 did not affect chow intake in *Chow/Chow* mice.

BD-1063 did affect body weight change in either *Chow/Chow* or *Chow/Palatable* groups [Dose: $F(2,44) = 0.48$, *n.s.*; Figure 3F Dose $\times$ Diet Group: $F(2,44) = 0.22$, *n.s.*].

4. Discussion

This study aimed to validate both face and convergent validity of a mouse model of intermittent access to a palatable diet. Our results show that, similar to what has been observed in an analogous model of palatable diet alternation in rats, mice show adaptations in feeding behavior characterized by overconsumption of the highly palatable diet and hypophagia of the less preferred standard chow diet. Overall, *Chow/Palatable* mice had higher cumulative food intake due to a relative larger magnitude of overconsumption of palatable food during the *P Phase* compared to the magnitude of chow underconsumption during the *C phase* (+36% and – 26% vs. *Chow/Chow* mice in the *P Phase* and *C Phase*, respectively). Additionally, within the first hour of renewed access to palatable food, *Chow/Palatable* mice exhibited excessive (up to 5 times greater) eating behavior compared to control animals, and this intake escalated over time from the initial access. It is interesting to note that this escalation of first hour intake occurred while the daily hyperphagia across weeks remained stable, suggesting a shift in the time course of excessive eating towards the beginning of renewed access, following removal of palatable food. This resembles the escalating patterns of excessive intake seen after deprivation from drugs of abuse (Heyser et al., 2003; O'Dell and Koob, 2007; Rodd et al., 2004), and have been recapitulated in other models of palatable food access (Avena et al., 2005; Cottone et al., 2008; Pinel and Huang, 1976; Wojnicki et al., 2006).

Feeding adaptations across phases were accompanied by similar oscillating patterns in body weight change and feed efficiency. Notably, during the initial weeks of diet cycling, cumulative body weight and feed efficiency of *Chow/Palatable* mice were significantly higher than *Chow/Chow* controls. However, these differences slowly decreased over time, so that the two experimental groups did not differ in cumulative body weight and feed efficiency starting from week 7 and week 4, respectively.

While the results shown here using the present mouse model of diet alternation well replicate previous observations in rat models, it is also important to underscore some important differences between the two species. Indeed, while alterations in food intake, body weight, and feed efficiency in the rat have been shown to develop slowly and progressively during the course of several weeks of diet alternation (Blasio et al., 2014a; Dore et al., 2014), here in mice we observed that alterations in food intake, body weight, and feed efficiency in the mouse were robust since the first switches in diet (either chow to palatable or palatable to chow). These results suggest that the behavioral outcomes in response to

changes in food palatability develop more vigorously and more quickly in mice than in rats. Additionally, we observed that the overall cumulative food intake is higher in *Chow/Palatable* mice since the beginning of diet cycling. Typically, no differences in cumulative intake are observed due to hyperphagia of the palatable diet being overridden by hypophagia of the chow diet (Dore et al., 2014).

Naltrexone, an opioid receptor antagonist, selectively and dose-dependently reduced palatable diet intake in *Chow/Palatable* mice, with no effects on body weight in either group. These results are consistent with previous observations, which show that pretreatment with naltrexone dose-dependently reduces binge eating in rats (Apfelbaum and Mandenoff, 1981; Blasio et al., 2014b). These effects are typically (Apfelbaum and Mandenoff, 1981; Rao et al., 2008), though not always (Blasio et al., 2014b), selective for highly palatable diets, and naltrexone is thought to exert its effects by reducing the hedonic properties of food (Giuliano and Cottone, 2015; Kelley et al., 2002; Le Merrer et al., 2009; Taha, 2010). Naltrexone and other opioid receptor antagonists have been investigated in clinical populations, with promising effects on reductions in food intake and hedonic responses to palatable food (de Zwaan and Mitchell, 1992; Ziauddeen et al., 2013). Currently, naltrexone is an approved pharmacotherapeutic agent for obesity used in combination with bupropion, a norepinephrine/dopamine reuptake inhibitor (Narayanaswami and Dwoskin, 2017). Mu-opioid receptor drugs have been studied extensively for their modulation of the hedonic properties of multiple drugs of abuse in both humans (Gianoulakis, 2004; Schmitz et al., 2001; Volpicelli et al., 1992) and animals (Giuliano et al., 2013; Moore and Lynch, 2015; Sabino et al., 2007).

SR141716A, a CB1 receptor antagonist/inverse agonist, also selectively blocked excessive eating of palatable food in *Chow/Palatable* mice; though body weight was dose-dependently reduced in both *Chow/Chow* and *Chow/Palatable* mice. These observations are consistent with palatable diet cycling models in rats (Dore et al., 2014), where SR141716A treatment also reduced excessive eating in the first hour of renewed access to palatable food and reduced body weight gain. SR141716A has been investigated for its anti-obesity effects (Christensen et al., 2007), though has been withdrawn from the market for severe psychiatric side effects, including increased anxiety and depressed mood, effects that have been recapitulated in rat models of disordered eating (Blasio et al., 2013; Blasio et al., 2014a). CB1 antagonists/inverse agonists, including SR141716A, are also being investigated for their therapeutic potential in treating other forms of addiction (Henderson-Redmond et al., 2016; Le Foll and Goldberg, 2005), as they have been shown to modulate a variety of behaviors induced by addictive drugs, such as cocaine (Marinho et al., 2015; Mereu et al., 2015), ethanol (Economidou et al., 2006), and nicotine (Cohen et al., 2005; Le Foll and Goldberg, 2004).

Pretreatment with the Sig-1 receptor antagonist BD-1063 also selectively reduced excessive eating of the *Chow/Palatable* diet group at the highest dose tested. Our results are in agreement with the previous observation that pretreatment with BD-1063 induced a selective, dose-dependent reduction of palatable food consumption in bingeing rats (Cottone et al., 2012). Though not yet tested in humans, Sig-1 receptor antagonism is a promising therapeutic target for compulsive eating (Cottone et al., 2012), as well as alcohol (Sabino

and Cottone, 2016; Sabino et al., 2011; Sabino et al., 2009a; Sabino et al., 2009b; Valenza et al., 2016) and drug consumption (Hiranita et al., 2010; Nguyen et al., 2005; Sabino et al., 2017; Takahashi et al., 2000).

The effects of the pharmacological treatments of naltrexone, SR171416A, and BD-1063 on excessive eating of palatable food in this mouse model of palatable diet cycling mirror those seen in related rat models of disordered eating (Blasio et al., 2014b; Cottone et al., 2012; Dore et al., 2014). The experiments presented here assessed acute response to drug treatment, and additional studies on effects of chronic administration are needed to further investigate the therapeutic potential of these medications in treating disordered eating behavior. Results from the present study suggest convergent validity in mice and rat models, supports the utility of this paradigm in mice for further studying the pharmacological and neurobiological mechanisms of hyperphagia and obesity.

5. Conclusions

In summary, our experiments provide evidence for a novel model of palatable diet alternation in mice that presents strong face and convergent validity. Refinement of the preclinical animal model repertoire represents a critical aspect in mimicking the complexity of disordered eating, as well as providing effective tools for screening novel pharmacological targets (Moore et al., 2017a).

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References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5. Washington, DC: 2013.
- Apfelbaum M, Mandenoff A. Naltrexone suppresses hyperphagia induced in the rat by a highly palatable diet. *Pharmacol Biochem Behav.* 1981; 15:89–91. [PubMed: 7291235]
- Avena NM, Gold MS. Variety and hyperpalatability: are they promoting addictive overeating? *American Journal of Clinical Nutrition.* 2011; 94:367–368. [PubMed: 21715513]
- Avena NM, Long KA, Hoebel BG. Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. *Physiol Behav.* 2005; 84:359–362. [PubMed: 15763572]
- Berthoud HR. The neurobiology of food intake in an obesogenic environment. *Proc Nutr Soc.* 2012; 71:478–487. [PubMed: 22800810]
- Blasio A, Iemolo A, Sabino V, Petrosino S, Steardo L, Rice KC, et al. Rimobabant precipitates anxiety in rats withdrawn from palatable food: role of the central amygdala. *Neuropsychopharmacology.* 2013; 38:2498–2507. [PubMed: 23793355]

- Blasio A, Rice KC, Sabino V, Cottone P. Characterization of a shortened model of diet alternation in female rats: effects of the CB1 receptor antagonist rimonabant on food intake and anxiety-like behavior. *Behav Pharmacol*. 2014a; 25:609–617. [PubMed: 25011007]
- Blasio A, Steardo L, Sabino V, Cottone P. Opioid system in the medial prefrontal cortex mediates binge-like eating. *Addict Biol*. 2014b; 19:652–662. [PubMed: 23346966]
- Brammer MK, Gilmore DL, Matsumoto RR. Interactions between 3,4-methylenedioxymethamphetamine and sigma1 receptors. *European Journal of Pharmacology*. 2006; 553:141–145. [PubMed: 17070798]
- Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet*. 2007; 370:1706–1713. [PubMed: 18022033]
- Cohen C, Perrault G, Griebel G, Soubrie P. Nicotine-associated cues maintain nicotine-seeking behavior in rats several weeks after nicotine withdrawal: reversal by the cannabinoid (CB1) receptor antagonist, rimonabant (SR141716). *Neuropsychopharmacology*. 2005; 30:145–155. [PubMed: 15292905]
- Cole JC, Littleton JM, Little HJ. Acamprosate, but not naltrexone, inhibits conditioned abstinence behaviour associated with repeated ethanol administration and exposure to a plusmaze. *Psychopharmacology (Berl)*. 2000; 147:403–411. [PubMed: 10672634]
- Cottone P, Sabino V, Steardo L, Zorrilla EP. Intermittent access to preferred food reduces the reinforcing efficacy of chow in rats. *Am J Physiol Regul Integr Comp Physiol*. 2008; 295:R1066–1076. [PubMed: 18667718]
- Cottone P, Wang X, Park JW, Valenza M, Blasio A, Kwak J, et al. Antagonism of sigma-1 receptors blocks compulsive-like eating. *Neuropsychopharmacology*. 2012; 37:2593–2604. [PubMed: 22713906]
- Davis C. From passive overeating to "food addiction": a spectrum of compulsion and severity. *ISRN Obes*. 2013; 2013:435027. [PubMed: 24555143]
- de Zwaan M. Binge eating disorder and obesity. *Int J Obes Relat Metab Disord*. 2001; 25(Suppl 1):S51–55. [PubMed: 11466589]
- de Zwaan M, Mitchell JE. Opiate antagonists and eating behavior in humans: a review. *J Clin Pharmacol*. 1992; 32:1060–1072. [PubMed: 1487543]
- Dol-Gleizes F, Paumelle R, Visentin V, Mares AM, Desitter P, Hennuyer N, et al. Rimonabant, a selective cannabinoid CB1 receptor antagonist, inhibits atherosclerosis in LDL receptor-deficient mice. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2009; 29:12–18.
- Dore R, Valenza M, Wang X, Rice KC, Sabino V, Cottone P. The inverse agonist of CB1 receptor SR141716 blocks compulsive eating of palatable food. *Addict Biol*. 2014; 19:849–861. [PubMed: 23587012]
- Duarte C, Alonso R, Bichet N, Cohen C, Soubrie P, Thiebot MH. Blockade by the cannabinoid CB1 receptor antagonist, rimonabant (SR141716), of the potentiation by quinolorane of food-primed reinstatement of food-seeking behavior. *Neuropsychopharmacology*. 2004; 29:911–920. [PubMed: 14694354]
- Dulloo AG, Montani JP. Pathways from dieting to weight regain, to obesity and to the metabolic syndrome: an overview. *Obesity Reviews*. 2015; 16(Suppl 1):1–6.
- Economidou D, Mattioli L, Cifani C, Perfumi M, Massi M, Cuomo V, et al. Effect of the cannabinoid CB1 receptor antagonist SR-141716A on ethanol self-administration and ethanol-seeking behaviour in rats. *Psychopharmacology (Berl)*. 2006; 183:394–403. [PubMed: 16261315]
- Escher T, Mittleman G. Schedule-induced alcohol drinking: non-selective effects of acamprosate and naltrexone. *Addiction Biology*. 2006; 11:55–63. [PubMed: 16759337]
- Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. *Appetite*. 2009; 52:430–436. [PubMed: 19121351]
- Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Archives of General Psychiatry*. 2011; 68:808–816. [PubMed: 21464344]
- Gianoulakis C. Endogenous opioids and addiction to alcohol and other drugs of abuse. *Curr Top Med Chem*. 2004; 4:39–50. [PubMed: 14754375]

- Giuliano C, Cottone P. The role of the opioid system in binge eating disorder. *CNS Spectr*. 2015; 20:537–545. [PubMed: 26499083]
- Giuliano C, Robbins TW, Wille DR, Bullmore ET, Everitt BJ. Attenuation of cocaine and heroin seeking by mu-opioid receptor antagonism. *Psychopharmacology (Berl)*. 2013; 227:137–147. [PubMed: 23299095]
- Hartz SM, Ben-Shahar Y, Tyler M. Logistic growth curve analysis in associative learning data. *Animal Cognition*. 2001; 3:185–189.
- Henderson-Redmond AN, Guindon J, Morgan DJ. Roles for the endocannabinoid system in ethanol-motivated behavior. *Prog Neuropsychopharmacol Biol Psychiatry*. 2016; 65:330–339. [PubMed: 26123153]
- Heyser CJ, Moc K, Koob GF. Effects of naltrexone alone and in combination with acamprosate on the alcohol deprivation effect in rats. *Neuropsychopharmacology*. 2003; 28:1463–1471. [PubMed: 12700689]
- Hiranita T, Soto PL, Tanda G, Katz JL. Reinforcing effects of sigma-receptor agonists in rats trained to self-administer cocaine. *J Pharmacol Exp Ther*. 2010; 332:515–524. [PubMed: 19892920]
- Hofmann W, Adriaanse M, Vohs KD, Baumeister RF. Dieting and the self-control of eating in everyday environments: an experience sampling study. *British Journal of Health Psychology*. 2014; 19:523–539. [PubMed: 23751109]
- Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M. Opioid modulation of taste hedonics within the ventral striatum. *Physiol Behav*. 2002; 76:365–377. [PubMed: 12117573]
- Kotagale NR, Mendhi SM, Aglawe MM, Umekar MJ, Taksande BG. Evidences for the involvement of sigma receptors in antidepressant like effect of quetiapine in mice. *European Journal of Pharmacology*. 2013; 702:180–186. [PubMed: 23399765]
- Laessle RG, Tuschl RJ, Kotthaus BC, Pirke KM. Behavioral and biological correlates of dietary restraint in normal life. *Appetite*. 1989; 12:83–94. [PubMed: 2764557]
- Le Foll B, Goldberg SR. Rimonabant, a CB1 antagonist, blocks nicotine-conditioned place preferences. *Neuroreport*. 2004; 15:2139–2143. [PubMed: 15486497]
- Le Foll B, Goldberg SR. Cannabinoid CB1 receptor antagonists as promising new medications for drug dependence. *J Pharmacol Exp Ther*. 2005; 312:875–883. [PubMed: 15525797]
- Le Merrer J, Becker JA, Befort K, Kieffer BL. Reward processing by the opioid system in the brain. *Physiol Rev*. 2009; 89:1379–1412. [PubMed: 19789384]
- Liu Y, Chen GD, Lerner MR, Brackett DJ, Matsumoto RR. Cocaine up-regulates Fra-2 and sigma-1 receptor gene and protein expression in brain regions involved in addiction and reward. *Journal of Pharmacology and Experimental Therapeutics*. 2005; 314:770–779. [PubMed: 15879001]
- Liu Y, Matsumoto RR. Alterations in fos-related antigen 2 and sigma1 receptor gene and protein expression are associated with the development of cocaine-induced behavioral sensitization: time course and regional distribution studies. *Journal of Pharmacology and Experimental Therapeutics*. 2008; 327:187–195. [PubMed: 18591217]
- Lowe MR, Doshi SD, Katterman SN, Feig EH. Dieting and restrained eating as prospective predictors of weight gain. *Frontiers in Psychology*. 2013; 4:577. [PubMed: 24032024]
- Marinho EA, Oliveira-Lima AJ, Santos R, Hollais AW, Baldaia MA, Wuo-Silva R, et al. Effects of rimonabant on the development of single dose-induced behavioral sensitization to ethanol, morphine and cocaine in mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015; 58:22–31. [PubMed: 25496830]
- Mela DJ. Determinants of food choice: relationships with obesity and weight control. *Obesity Research*. 2001; 9(Suppl 4):249S–255S. [PubMed: 11707550]
- Mereu M, Tronci V, Chun LE, Thomas AM, Green JL, Katz JL, et al. Cocaine-induced endocannabinoid release modulates behavioral and neurochemical sensitization in mice. *Addict Biol*. 2015; 20:91–103. [PubMed: 23910902]
- Moore CF, Lynch WJ. Alcohol preferring (P) rats as a model for examining sex differences in alcohol use disorder and its treatment. *Pharmacol Biochem Behav*. 2015; 132:1–9. [PubMed: 25712173]
- Moore CF, Panciera JJ, Sabino V, Cottone P. Neuropharmacology of compulsive eating. *Phil Trans Soc B*. 2017a In press.

- Moore CF, Sabino V, Koob GF, Cottone P. Neuroscience of Compulsive Eating Behavior. *Frontiers in Neuroscience*. 2017b; 11
- Moore CF, Sabino V, Koob GF, Cottone P. Pathological Overeating: Emerging Evidence for a Compulsivity Construct. *Neuropsychopharmacology*. 2017c; 42:1375–1389. [PubMed: 27922596]
- Morris MJ, Beilharz JE, Maniam J, Reichelt AC, Westbrook RF. Why is obesity such a problem in the 21st century? The intersection of palatable food, cues and reward pathways, stress, and cognition. *Neurosci Biobehav Rev*. 2015; 58:36–45. [PubMed: 25496905]
- Moslehi A, Nabavizadeh F, Dehpour AR, Tavanga SM, Hassanzadeh G, Zekri A, et al. Naltrexone attenuates endoplasmic reticulum stress induced hepatic injury in mice. *Acta Physiologica Hungarica*. 2014; 101:341–352. [PubMed: 25183508]
- Narayanaswami V, Dwoskin LP. Obesity: Current and potential pharmacotherapeutics and targets. *Pharmacol Ther*. 2017; 170:116–147. [PubMed: 27773782]
- Nguyen EC, McCracken KA, Liu Y, Pouw B, Matsumoto RR. Involvement of sigma (sigma) receptors in the acute actions of methamphetamine: receptor binding and behavioral studies. *Neuropharmacology*. 2005; 49:638–645. [PubMed: 15939443]
- Nguyen L, Robson MJ, Healy JR, Scandinaro AL, Matsumoto RR. Involvement of sigma-1 receptors in the antidepressant-like effects of dextromethorphan. *Public Library of Science One*. 2014; 9:e89985. [PubMed: 24587167]
- O'Dell LE, Koob GF. 'Nicotine deprivation effect' in rats with intermittent 23-hour access to intravenous nicotine self-administration. *Pharmacol Biochem Behav*. 2007; 86:346–353. [PubMed: 17292952]
- Pankevich DE, Teegarden SL, Hedin AD, Jensen CL, Bale TL. Caloric restriction experience reprograms stress and orexigenic pathways and promotes binge eating. *J Neurosci*. 2010; 30:16399–16407. [PubMed: 21123586]
- Pinel JP, Huang E. Effects of periodic withdrawal on ethanol and saccharin selection in rats. *Physiol Behav*. 1976; 16:693–698. [PubMed: 981364]
- Polivy J, Herman CP. Dieting and bingeing. A causal analysis. *American Psychologist*. 1985; 40:193–201. [PubMed: 3857016]
- Rao RE, Wojnicki FH, Coupland J, Ghosh S, Corwin RL. Baclofen, raclopride, and naltrexone differentially reduce solid fat emulsion intake under limited access conditions. *Pharmacol Biochem Behav*. 2008; 89:581–590. [PubMed: 18353432]
- Rodd ZA, Bell RL, Sable HJ, Murphy JM, McBride WJ. Recent advances in animal models of alcohol craving and relapse. *Pharmacol Biochem Behav*. 2004; 79:439–450. [PubMed: 15582015]
- Sabino V, Cottone P. *Handbook of Experimental Pharmacology*. Springer; Berlin, Heidelberg: 2016. Sigma Receptors and Alcohol Use Disorders; p. 1-18.
- Sabino V, Cottone P, Blasio A, Iyer MR, Steardo L, Rice KC, et al. Activation of sigma-receptors induces binge-like drinking in Sardinian alcohol-preferring rats. *Neuropsychopharmacology*. 2011; 36:1207–1218. [PubMed: 21346735]
- Sabino V, Cottone P, Steardo L, Schmidhammer H, Zorrilla EP. 14-Methoxymetopon, a highly potent mu opioid agonist, biphasically affects ethanol intake in Sardinian alcoholpreferring rats. *Psychopharmacology (Berl)*. 2007; 192:537–546. [PubMed: 17345066]
- Sabino V, Cottone P, Zhao Y, Iyer MR, Steardo L Jr, Steardo L, et al. The sigma receptor antagonist BD-1063 decreases ethanol intake and reinforcement in animal models of excessive drinking. *Neuropsychopharmacology*. 2009a; 34:1482–1493. [PubMed: 18946467]
- Sabino V, Cottone P, Zhao Y, Steardo L, Koob GF, Zorrilla EP. Selective reduction of alcohol drinking in Sardinian alcohol-preferring rats by a sigma-1 receptor antagonist. *Psychopharmacology (Berl)*. 2009b; 205:327–335. [PubMed: 19440699]
- Sabino V, Hicks C, Cottone P. Sigma Receptors and Substance Use Disorders. *Adv Exp Med Biol*. 2017; 964:177–199. [PubMed: 28315272]
- Schmitz JM, Stotts AL, Rhoades HM, Grabowski J. Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addict Behav*. 2001; 26:167–180. [PubMed: 11316375]
- Schulte EM, Avena NM, Gearhardt AN. Which foods may be addictive? The roles of processing, fat content, and glycemic load. *PLoS One*. 2015; 10:e0117959. [PubMed: 25692302]

- Stafford AM, Anderson SM, Shelton KL, Brunzell DH. Oral operant ethanol self-administration in the absence of explicit cues, food restriction, water restriction and ethanol fading in C57BL/6J mice. *Psychopharmacology (Berlin)*. 2015; 232:3783–3795. [PubMed: 26268145]
- Taha SA. Preference or fat? Revisiting opioid effects on food intake. *Physiol Behav*. 2010; 100:429–437. [PubMed: 20211638]
- Takahashi S, Miwa T, Horikomi K. Involvement of sigma 1 receptors in methamphetamine-induced behavioral sensitization in rats. *Neurosci Lett*. 2000; 289:21–24. [PubMed: 10899399]
- Valenza M, DiLeo A, Steardo L, Cottone P, Sabino V. Ethanol-related behaviors in mice lacking the sigma-1 receptor. *Behav Brain Res*. 2016; 297:196–203. [PubMed: 26462569]
- Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry*. 1992; 49:876–880. [PubMed: 1345133]
- Ward SJ, Walker EA, Dykstra LA. Effect of cannabinoid CB1 receptor antagonist SR141716A and CB1 receptor knockout on cue-induced reinstatement of Ensure and corn-oil seeking in mice. *Neuropsychopharmacology*. 2007; 32:2592–2600. [PubMed: 17392737]
- Wiley JL, Burston JJ, Leggett DC, Alekseeva OO, Razdan RK, Mahadevan A, et al. CB1 cannabinoid receptor-mediated modulation of food intake in mice. *British Journal of Pharmacology*. 2005; 145:293–300. [PubMed: 15778743]
- Wojnicki FH, Roberts DC, Corwin RL. Effects of baclofen on operant performance for food pellets and vegetable shortening after a history of binge-type behavior in non-food deprived rats. *Pharmacol Biochem Behav*. 2006; 84:197–206. [PubMed: 16782181]
- Ziauddeen H, Chamberlain SR, Nathan PJ, Koch A, Maltby K, Bush M, et al. Effects of the mu-opioid receptor antagonist GSK1521498 on hedonic and consummatory eating behaviour: a proof of mechanism study in binge-eating obese subjects. *Mol Psychiatry*. 2013; 18:1287–1293. [PubMed: 23147384]

Highlights

- Mice were provided intermittent, *ad libitum* access to a palatable diet
- Mice escalated palatable diet intake over time and displayed chow diet hypophagia
- Naltrexone, SR141716A, and BD-1063 reduced overconsumption of the palatable diet
- Palatable diet cycling in mice is a useful model to study disordered eating

Figure 1.

Effects of intermittent, extended access to a palatable diet on (A) average daily food intake, (B) cumulative food intake, (C) average daily body weight changes, (D) cumulative body weight change, (E) average daily feed efficiency, and (F) cumulative feed efficiency in mice ($N=9$ Chow/Chow; $N=16$ Chow/Palatable). Values for *C* Phase represent the average of 2 days with access to chow diet. Data represent the Mean ($M \pm SEM$). Symbols indicate significant difference between diet groups * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, relative to Chow/Chow diet group.

Figure 2.

(A) Effects of intermittent, extended access to a palatable diet on food intake during the first hour of *P Phase* (when *Chow/Palatable* mice have access to the palatable diet and *Chow/Chow* mice have access to the standard diet: $N=16$ and 9 , respectively). (B) Sigmoidal regression of palatable diet intake during the first hour of *P Phase* in *Chow/Palatable* mice. $N = 25$; data represent the Mean ($\pm$ SEM). Symbols indicate significant difference between diet groups * $p<0.05$, *** $p<0.001$.

Figure 3.

Effects of pretreatment (–30 min) with the opioid receptor antagonist naltrexone on 1-hour food intake (A) and body weight change (D). Effects of pretreatment (–30 min) with the CB1 receptor antagonist/inverse agonist SR141716 (0, 3 mg/kg, 10 mg/kg, *i.p.*) on 1-hour food intake (B) and body weight change (E). Effects of pretreatment (–15 min) with the Sig-1 receptor antagonist BD-1063 (0, 10 mg/kg, 30 mg/kg, *i.p.*) on 1-hour food intake (C) and body weight change (F). $N=24$ mice per group. Data represent the Mean ($\pm$ SEM). Symbols indicate significant difference either from vehicle-treated mice * $p<0.05$, *** $p<0.001$ or from the low dose-treated mice of the same diet group ## $p<0.01$, ### $p<0.001$.