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# Selection of a palatable dietary option is not preferentially reduced by cannabinoid CB1 receptor antagonist AM251 in female C57Bl/6J mice

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ABSTRACT

We previously showed in female rats that administration of the cannabinoid CB1 receptor antagonist AM251 reduced energy intake by selectively decreasing consumption of a palatable dietary option in comparison to a standard maintenance chow. In the present study we sought to generalize these findings to mice. We presented 6 week old female C57Bl/6J mice with daily 8 h access to a sugar fat whip dietary option along with ad libitum access to moist chow. Mice were injected daily with either vehicle (equal parts polyethylene glycol and saline, 2 ml/kg) or one of three doses of AM251 (1, 3, or 10 mg/kg). Food intake and body weight were measured daily for 21 days. Although 8 h access to sugar fat whip did not induce overconsumption in female mice, AM251 reduced their energy intake and body weight in a dose-dependent manner. The decrease in energy intake occurred for both chow and sugar fat whip. This difference from results in rats suggests that the effect of AM251 on palatable food intake may only be evident in models that induce overconsumption and/or that rats and mice may react differently to CB1 receptor antagonists.

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## 1. Introduction

Obesity results from high energy intake in relation to expenditure. Although a decrease in energy expenditure contributes to this imbalance, the progressive increase in access to and availability of inexpensive, high energy food is correlated with the increase in the incidence of obesity in humans (Stein and Colditz, 2004). These environmental factors interact with multiple gene families that impact food intake, diet selection, body weight gain, and, ultimately, the prevalence of obesity (Drenowski and Levine, 2003; Bray and Champagne, 2003; Ravussin and Bogardus, 2000). Rodent models of exposure to palatable foods, often but not always leading to overeating and obesity, have been pivotal in elucidating behavioral and physiological factors involved in maladaptive eating patterns of humans (Avena et al., 2008; Cottone et al., 2008; Sclafani and Springer, 1976). We have previously reported that female Sprague–Dawley rats given ad libitum access to a conventional maintenance diet and also given daily access to a palatable but nutritionally-incomplete dietary option composed of sugar and fat consumed more energy and gained more weight than rats given only the nutritionally-complete diet (Mathes et al., 2008). Since this protocol provides animals with a choice between two diets, we suggested that it may have benefits compared with similar models that induce obesity by providing access to a single high fat diet (Levin, 2005).

We used this protocol to assess the effect of cannabinoid type-1 receptor (CB1R) antagonists, Rimonabant (formerly SR141716A) and AM251, on overconsumption and diet selection in rats (Mathes et al., 2008). CB1R antagonists reduce food intake, and it is speculated that the hypophagia is mediated via a temporary decrease in the perception of the hedonic value of the food. This is supported by reports using both brief access (Higgs et al., 2003; Jarrett et al., 2007) and consummatory (Arnone et al., 1997; Freedland et al., 2000; Koch, 2003; Miller et al., 2004; Simiand et al., 1998; Ward and Dykstra, 2005) protocols. Our study using the aforementioned choice protocol supported these results: rats injected with Rimonabant or AM251 ate less energy than those rats injected with vehicle, and this reduction was selective to the sweet and fatty dietary option.

Since murine models allow examination of gene families in a manner unavailable in rats, we sought to extend this protocol to mice. Although C57Bl/6J mice are known to be more responsive to sugar and fat and more prone to obesity when provided with a high fat diet than many other mouse strains (Collins et al., 2004; Matyskova et al., 2007; Sclafani and Glendining, 2005), we did not see an increase in caloric intake in female C57Bl/6J mice that were presented with a sweet and fatty dietary option for various durations (Mathes et al., 2007; Mathes, 2008). This discrepancy presented the opportunity to examine if the decrease in the intake of palatable foods following CB1R antagonist administration is seen only in conditions that induce overconsumption. We define overconsumption as an increase in energy intake from

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a palatable dietary option that is not compensated for by a reduction in maintenance diet intake.

The few studies that have examined the effect of repeated CB1R antagonist administration on energy intake in mice provided with a high fat palatable diet showed a sustained decrease in caloric intake and body weight gain (Hildebrandt et al., 2005; Ravinet-Trillou et al., 2004); however, these results are from mice given access to only one diet. Only one study of which we know has explored diet selection within groups of mice (South et al., 2007). They reported that male C57Bl/6J mice injected with AM251 showed reduced preference for a nutritionally-complete high fat diet over a nutritionally-complete low fat diet, which were both provided ad libitum. We hypothesize that the results of the current study with mice will be similar to these and to our previous results seen in rats using a choice between a nutritionally-complete diet and time limited access to a palatable but nutritionally-incomplete dietary option.

## 2. Methods

### 2.1. Animals and housing

The experiment was conducted using 6 week old female C57Bl/6J mice (Jackson Labs, Bar Harbor, ME) that weighed 16–20 g at the start of the experiment. Female C57Bl/6J mice were used because in our previous studies we used female rats (Mathes et al., 2008) or female mice (Mathes et al., 2007; Mathes, 2008). Data were taken without assessing the stage of the estrous cycle; visual inspection of the data revealed no systematic differences within or among group data as a result of such cyclicity. All mice were individually housed in standard polycarbonate tubs containing a 2–3 cm layer of bedding (SaniChips, Teklad, Madison, WI) and provided with material for nest building (Nestlet, AnCare, Bellmore, NY). They were provided with ad libitum access to tap water and to a standard maintenance diet as described below. The vivarium was temperature and humidity controlled (23 ± 2 °C, 45–55%) and on a 12 h reverse light cycle (lights off from 11:30–23:30 h). All measures were taken during the dark cycle, which is the time when mice are most active and consume most of their daily food. All animal procedures were approved by the University of Florida IACUC.

### 2.2. Diets

Moist chow was used as the ad libitum maintenance diet in the study because it is less easily spilled than powdered chow and because the moist texture reduces some differences between the maintenance diet and the palatable dietary option (see below). Moist chow (1.67 kcal/g) was made by mixing powdered standard chow (Purina 5001) with an equal amount of tap water; this was allowed to come to room temperature and was spooned into 10 ml glass beakers. A beaker of moist chow was attached to a metal stirrup and suspended in the left corner of each cage. Fresh jars of moist chow were provided daily. Food consumption was measured for an 8 day period before initiation of the experimental phase of the study to ensure stability of intake. Mice were assigned to groups based on intakes during the baseline period such that large and small eaters were equally represented in each group.

Some mice were also presented with a palatable dietary option throughout the study. The palatable food source used was a sugar fat whip (7.35 kcal/g) that was made by mixing two parts softened vegetable shortening with one part sugar. Both commodities were generic brands purchased from a local supermarket (Publix). Sugar fat whip was allowed to come to room temperature and was spooned into 10 ml glass beakers. The beakers were attached to a metal stirrup and hung in the right corner of each cage. Mice were provided with 24 h access to sugar fat whip before the start of the experiment to reduce neophobia; intakes during this time were equivalent between groups. Fresh sugar fat whip was provided daily.

### 2.3. Experimental design

The experiment sought to examine in female C57Bl/6J mice the effect of options between diets and administration of AM251, a CB1R antagonist, on the consumption and selection of the diets. Four groups of mice ($n = 8$) received 8 h nocturnal access (1130–1930 h) to the more palatable dietary option (sugar fat whip) daily in addition to ad libitum access to moist chow. Mice received daily injections of either one of three doses of AM251 (1, 3, or 10 mg/kg IP) or vehicle (equal parts polyethylene glycol and saline, 2 ml/kg IP) 30 min prior to access to the diet options. The doses of AM251 were chosen based on our previous studies with rats (Mathes et al., 2008) and in the range used by other studies (South et al., 2007). Sugar fat whip and moist chow intakes were measured by subtracting the remaining weight of the diet from that originally presented. Spillage occurred infrequently, but when by visual inspection it appeared to be greater than 1 g, the data from that mouse for that day were excluded from study. All of the data from one mouse in the group injected with 3 mg/kg AM251 was removed from study due to consistent spillage of moist chow. The body weight of each mouse was measured daily prior to AM251 injection. Total energy intakes, as well as individual energy intakes from each dietary option, and body weight change from baseline were calculated daily for 21 days.

### 2.4. Drugs

AM251 was purchased from Tocris (Ellisville, MO). AM251 was dissolved in polyethylene glycol (Sigma Chemical Co., St. Louis, MO; molecular weight = 400) and then an equal amount of saline was added. The drug precipitated slowly in this vehicle, so was sonicated immediately prior to injection to provide a suitable suspension in which no precipitate was observed at the time of the injection. We have previously reported that this vehicle has little effect on food intake in this protocol (Mathes et al., 2008). Injections were given in volumes of 0.02 ml / 10 g body weight. AM251 has been shown to possibly have inverse agonist properties (Gatley et al., 1996), but for simplicity it will be referred to as an antagonist in this manuscript.

### 2.5. Statistical analysis

All data were analyzed using SPSS (Chicago, IL). The average daily total energy intakes, as well as the component intakes from each diet option were analyzed via two-way ANOVA with groups and days as main factors. When the analysis revealed a significant ($p \leq 0.05$) effect of days and / or a significant group × day interaction, Tukey post hoc comparisons were used to examine daily differences among groups and within-group differences across days. The cumulative body weight changes from the end of the first and end of the last day of the experiment were analyzed with two-way ANOVA and significant differences among or within groups were further analyzed with Tukey post hoc comparisons of each day's average cumulative body weight change.

## 3. Results

The average cumulative daily total energy intakes across the days of the experiment are presented in panel (a) of Fig. 1. Significant effects of group ($F[3,28] = 44.54$, $p < 0.001$) and days ($F[20,28] = 3.67$, $p < 0.001$) were present, but there was no group × day interaction ($F[60,560] = 0.61$, $p = 0.992$). The average daily intakes across the entire period are shown in Table 1. Significant differences in total energy intakes among the groups were present on days 1, 4–7, 10, 13, 15–18, 20, and 21. On days 6 and 18, mice in all of the drug groups ate significantly less than

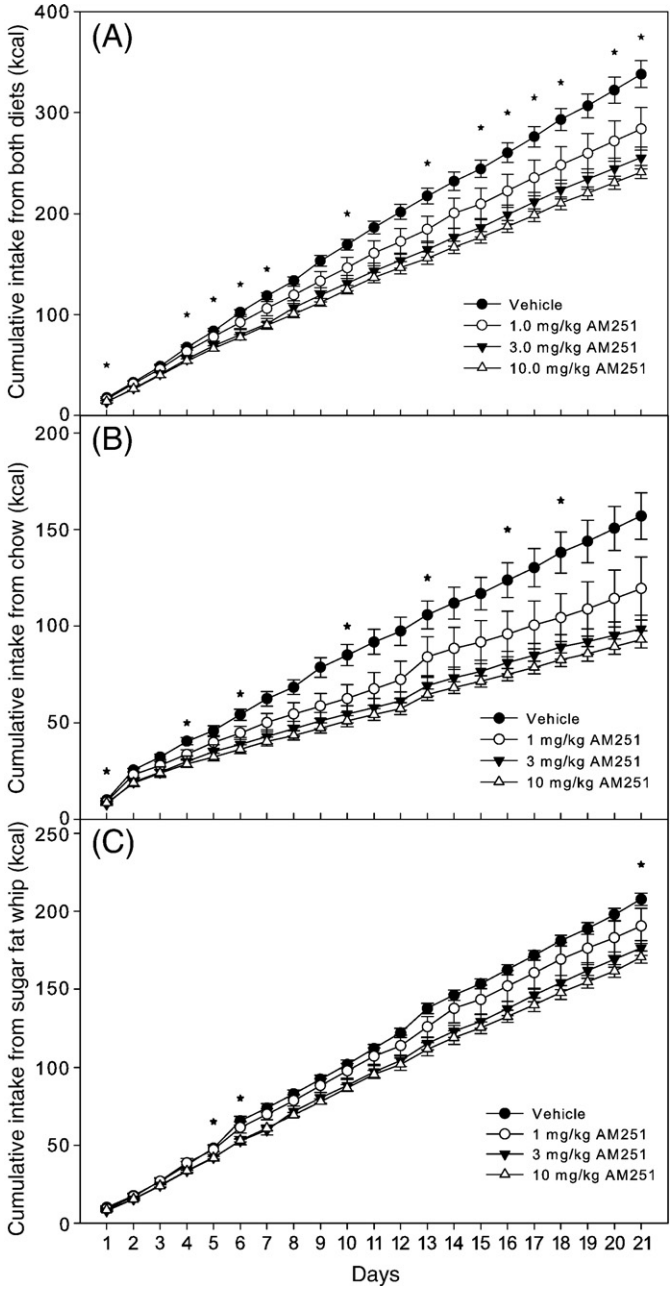


**Fig. 1.** Cumulative energy intakes of mice across the 21 days of testing (mean ± SE kcal; $n = 7–8$) during which mice were injected with either vehicle or one of three doses of CB1 receptor antagonist AM251 while provided with ad libitum access to a moist chow maintenance diet and 8 h nocturnal access to a sugar fat whip palatable dietary option. Panel A shows cumulative total energy intakes from both diets; panel B shows cumulative energy intakes from moist chow alone; panel C shows cumulative energy intakes from sugar fat whip alone. Stars posted above data points represent days during which average intakes on that day were significantly different among groups ($p<0.05$). The specific group differences are reported in the results section.

mice injected with vehicle. On days 1, 3, 4, and 20, mice injected with 3 or 10 mg/kg AM251 ate less than mice injected with vehicle. On days 5, 7, 16, and 17, mice injected with 10 mg/kg AM251 ate less than mice injected with vehicle. On days 10 and 21, mice injected with 3 mg/kg AM251 ate less than mice injected with vehicle. On day 15, mice injected with 1 mg/kg AM251 ate less than mice injected with vehicle.

The average cumulative daily energy intakes from moist chow across the days of the experiment are presented in panel (b) of Fig. 1. Significant effects of group ($F[3,28] = 45.17$, $p<0.001$) and day ($F[20,28] = 2.294$, $p = 0.001$) were present, but there was no group × day interaction ($F[60,560] = 0.581$, $p = .995$). The average intakes across the entire

**Table 1**
Average daily total intakes from both diet options, daily individual intakes from moist chow and sugar fat whip, and cumulative body weight changes.

| | AM251 | | | |
|---|---|---|---|---|
| | 0.0 mg/kg | 1.0 mg/kg | 3.0 mg/kg | 10.0 mg/kg |
| Total intake | 16.13 ± 0.30 | 13.54 ± 0.30 | 12.16 ± 0.30 | 11.58 ± 0.32 |
| Moist chow intake | 6.91 ± 0.21 | 4.93 ± 0.21 | 4.08 ± 0.21 | 3.76 ± 0.22 |
| Sugar fat whip intake | 9.21 ± 0.22 | 8.62 ± 0.22 | 8.08 ± 0.22 | 7.81 ± 0.23 |
| Body weight change | 1.68 ± 0.06 | 0.96 ± 0.06 | 0.36 ± 0.06 | 0.18 ± 0.06 |

Intake values ($n = 8$) are expressed as mean ± SE in kilocalories and body weight change values are expressed as cumulative mean ± SE in grams.

period are shown in Table 1. Significant differences in energy intakes from moist chow were present among groups on days 1, 4, 6, 10, 13, 16, and 18. On days 4, 6, and 18, mice in all of the drug groups ate significantly less moist chow than mice injected with vehicle. On days 10 and 13, mice injected with 3 or 10 mg/kg AM251 ate less moist chow than mice injected with vehicle. On day 16, mice injected with 1 or 10 mg/kg AM251 ate less moist chow than mice injected with vehicle. Tukey analysis revealed no differences among groups on day 1, perhaps because the one-way ANOVA was only marginally significant ($F[3,28] = 3.001$, $p = 0.048$).

The average cumulative daily energy intakes from sugar fat whip across the days of the experiment are presented in panel (c) of Fig. 1. Significant effects of group ($F[3,28] = 7.78$, $p<0.001$) and day ($F[20,28] = 2.97$, $p<0.001$) were present, but there was no group × day interaction ($F[60,560] = .744$, $p = 0.923$). The average intakes across the entire period are presented in Table 1. Significant differences in energy intakes from sugar fat whip were present among groups on days 5, 6, and 21. On day 5, mice in all of the drug groups ate significantly less sugar fat whip than mice injected with vehicle. On day 6, mice injected with 3 or 10 mg/kg AM251 ate less sugar fat whip than mice injected with vehicle. On day 21, mice injected with 3 mg/kg AM251 ate less SFW than mice injected with vehicle.

The cumulative average body weight changes from baseline across days are presented in Fig. 2. Significant effects of group ($F[3,28] = 142.6$, $p<0.001$) and day ($F[3,28] = 7.5$, $p<0.001$) were present, but there was no group × day interaction ($F[60,560] = 0.5$, $p>0.9$). Significant differences in body weight changes among groups were present on all days. On days 1 and 2, mice injected with 3 or 10 mg/kg AM251 gained less weight than mice injected with 1 mg/kg AM251, which gained less weight than mice injected with vehicle. On days 3 and 5–19, mice injected with 3 or 10 mg/kg AM251 gained less weight than mice

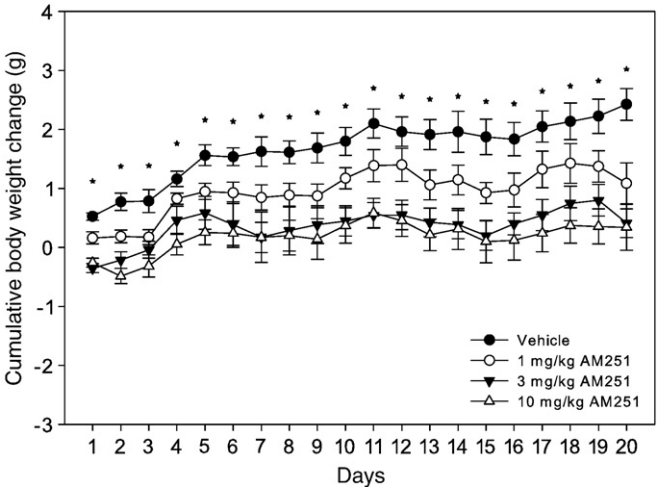


**Fig. 2.** Cumulative change in body weight in mice (mean ± SE g; $n = 7–8$) on the drug regimen and diet protocol described in the caption for Fig. 1. Stars posted above data points represent days during which average cumulative weight gain was significantly different among groups. These differences are specified in the results section.

injected with vehicle. On day 4, mice injected with 10 mg/kg AM251 gained less weight than mice injected with vehicle. On day 20, mice in all the drug groups gained less weight than mice injected with vehicle.

## 4. Discussion

In this study, female mice were provided with ad libitum access to a nutritionally-complete maintenance diet and time limited access to a sweet and fatty dietary option to assess the extent to which mice would consume each diet. Mice avidly consumed the sugar fat whip, ingesting nearly $\frac{2}{3}$ of their total energy intake solely from this source; however, mice sufficiently reduced their intake of moist chow such that the total amount of energy consumed by mice in the presence of the two diets was equivalent to the amount consumed when only the maintenance diet was present. This is consistent with our previous studies using mice (Mathes et al., 2007; Mathes, 2008), but is in contrast data from female Sprague–Dawley rats, which do not reduce their intake of moist chow to compensate fully for the energy consumed from sugar fat whip (Mathes et al., 2008).

This study also examined the effect of CB1R antagonist AM251 on energy intake, body weight gain, and choice between diets. Studies in a wide array of species and using many techniques show that CB1R antagonists decrease energy intake by selectively reducing consumption of palatable diets (Arnone et al., 1997; Freedland et al., 2000; Koch, 2003; Mathes et al., 2008; Miller et al., 2004; Simiand et al., 1998; Ward and Dykstra, 2005), while other studies show suppression of bland diets (Colombo et al., 1998; Rowland et al., 2001) and equal suppression of diets of varying palatability (Foltin and Haney, 2007; Gessa et al., 2006; McLaughlin et al., 2003; Verty et al., 2004). In the present study, mice injected with AM251 consumed less energy than mice injected with vehicle, but this decrease resulted from reductions in intakes from both dietary options. This differs from a study in which AM251 reduced the total energy intakes of mice given a choice between ad libitum access to a nutritionally-complete high fat diet and a nutritionally-complete low fat diet by specifically reducing consumption of the high fat diet (South et al., 2007). This may be due to the provision of a choice between one energy-dilute nutritionally-complete diet and one energy dense dietary option compared to access to two nutritionally-complete diets of similar energy densities or the time limited availability of the dietary option compared to ad libitum access. Also, we used female mice that had been fed only moist chow prior to AM251 administration compared to male mice that had been provided with a choice between two diets for a week prior to injection with AM251, and so experience with high energy diets and an obese state may have impacted the results.

The current finding also differ from our results in which female rats given dietary options and injected with Rimonabant or AM251 consumed less energy than rats injected with vehicle, with this decrease being specific to the consumption of sugar fat whip. In fact, in our current study, more variability was seen in daily intakes from moist chow than from sugar fat whip. It seems that mice are able to accurately compensate for calories when choices are presented and this may affect the manner in which AM251 impinges on choice between diets and energy intake. If, as some studies suggest, the CB1R system does primarily modulate the intake of palatable foods, especially in situations in which there is a choice between commodities, the failure of AM251 to consistently reduce intake of sugar fat whip in mice may suggest that mice do not find this palatable dietary option as appealing as do rats. However, many other studies suggest that the CB system affects satiety or the amount of work an animal will perform to obtain a commodity (Escarten-Perez et al., 2009; Rasmussen and Huskinson, 2008; Sink et al., 2008). Future work using brief access tests or methods that bypass taste via gastric catheters, as well as operant techniques in economic paradigms may be instructive to further explore these species differences. It is also possible that separate CB1R populations may mediate intake and body weight effects of AM251, and that this may be achieved to a different degree in rats and mice; however, this question is beyond the scope of this study.

The differences between our studies with female C57Bl/6J mice and Sprague–Dawley rats (Mathes et al., 2008) and between our study using female mice and other studies with male mice (South et al., 2007) may suggest that some of the inconsistency in the literature exploring the action of CB1R antagonists may be due to species differences, sex differences, or a combination of these factors coupled with differences in diet regimens. Species differences have been reported with other drugs and receptor systems. For example, a single peripheral injection of PYY decreases food intake in mice but not in rats (Vrang et al., 2006), peripheral injection of ANG II does not induce drinking in mice as it does rats (Crews and Rowland, 2005), and CCK deficiency results in obesity in rats but not mice (Bi et al., 2007). Species differences in regulation, preference, and diet selection should be explored more in depth in future studies and taken into consideration when interpreting past literature.

## 5. Conclusions

Cannabinoid CB1 receptor antagonist AM251 reduced energy intake and body weight in female C57Bl/J6 mice, but this reduction was not specific to a palatable dietary option, as seen previously in male mice (South et al., 2007) and female rats (Mathes et al., 2008). This may be because the choice protocol that we used failed to produce overconsumption in mice, which we define as an increase in energy intake from one dietary option that is not sufficiently compensated for by a reduction in intake of the other diet. It seems that female C57Bl/6J mice may be better at regulating energy intake than female Sprague–Dawley rats, and these behavioral differences must be considered when selecting the appropriate species for modeling aspects of human behavior. It may also be that this palatable dietary option is not as appealing to mice as it is to rats, and thus test diets must also be carefully selected for appropriateness and ability to generalize when designing protocols for diet induced obesity. Since rats exhibit hyperphagia in the presence of a sweet fatty food and respond to CB1R antagonists in a manner similar to humans, it could be argued that rats are a better species in which to study diet induced obesity and the effect of CB1R antagonists on overconsumption and diet selection. Although mouse models offer tremendous insight into the genetics of feeding behavior, care must be taken that the behavior of the species used in experiments is similar to that which it is supposed to model.

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