Rimonabant Prevents Additional Accumulation of Visceral and Subcutaneous Fat During High-Fat Feeding In Dogs


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Abstract

We investigated whether rimonabant, a type 1 cannabinoid receptor antagonist, reduces visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in dogs maintained on a hypercaloric high-fat diet (HHFD). To determine whether energy expenditure contributed to body weight changes we also calculated resting metabolic rate. Twenty male dogs received either rimonabant (1.25 mg · kg\(^{-1} \cdot d^{-1}\), orally; \(n = 11\)) or placebo (\(n = 9\)) for 16 weeks, concomitant with a HHFD. VAT, SAT and non-fat tissue were measured by magnetic resonance imaging. Resting metabolic rate was assessed by indirect calorimetry. By week 16 of treatment, rimonabant dogs lost 2.5% of their body weight (\(P = 0.029\)), while in placebo dogs body weight increased by 6.2% (\(P < 0.001\)). Rimonabant reduced food intake (\(P = 0.027\)), concomitant with a reduction of SAT by 19.5% (\(P < 0.001\)). In contrast with the VAT increase with placebo (\(P < 0.01\)), VAT did not change with rimonabant. Non-fat tissue remained unchanged in both groups. Body weight loss was not associated with either resting metabolic rate (\(R^2 = 0.24\); \(P = 0.154\)) or food intake (\(R^2 = 0.24\); \(P = 0.166\)). In conclusion, rimonabant reduced body weight together with a reduction in abdominal fat, mainly due to SAT loss. Body weight changes were not associated with either resting metabolic rate or food intake. The findings provide evidence of a peripheral effect of rimonabant to reduce adiposity and body weight, possibly through a direct effect on adipose tissue.

Keywords: Adipose tissue, Body weight, Energy expenditure, Magnetic resonance, Resting metabolic rate
Introduction

The association among body fat accumulation, insulin resistance and other metabolic disorders, including type 2 diabetes, is well documented (3, 13, 19, 26). Obesity is a known risk factor for cardiovascular diseases, cancer, insulin resistance and the development of type 2 diabetes, this latter being the 5th leading cause of death in the United States (American Diabetes Association) and a growing problem worldwide (46). Of recent interest in this regard is the cannabinoid system and its role in the regulation of metabolism, body weight and energy expenditure (8, 33). One of the compounds which can affect obesity is rimonabant, a selective type 1 cannabinoid receptor (CB1R) antagonist (7, 34, 39). Rimonabant has been reported to decrease appetite and body weight, though the former effect seems to be transient and might not explain the sustained body weight loss (9, 11, 35, 36).

Studies conducted in rodents have shown that rimonabant decreases adiposity in different regions of the body. Obese mice treated with rimonabant decreased epididymal, peri-renal and lumbar fat depots (36) after 40-days of treatment. Similarly, rats treated with rimonabant for 10-14 days showed a decrease in total body fat (9) and subcutaneous, retroperitoneal, mesenteric and epididymal fat (11). A recent report demonstrates a significant reduction in visceral fat in mice treated with rimonabant for 6 weeks concomitant with a candy diet (16). However, what constitutes true visceral fat in the mouse model remains to be clearly identified.

To date, human studies testing the effect of rimonabant on obesity have demonstrated a significant reduction in waist circumference (7, 34, 43), which serves as a surrogate of
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visceral adiposity. Increased fat accumulation in the abdomen, particularly visceral adiposity, has been associated with a variety of metabolic abnormalities including insulin resistance and cardiovascular diseases (4, 14, 30, 42, 44). Interestingly, dogs, unlike rodents, have the typical abdominal fat compartments seen in humans, i.e., clearly defined as visceral and subcutaneous fat depots. These compartments are enhanced in dogs after a prolonged high-fat diet (24, 25) and are associated with the canine metabolic syndrome. Thus, it is of interest to study the effects of a cannabinoid antagonist in an animal model with fat compartments similar to humans in order to gain insight into possible therapies for fat deposition.

In this study, we monitored the effect of rimonabant treatment on fat distribution in the abdominal trunk of dogs maintained on a high-fat diet. In addition, since obesity results from an imbalance between caloric intake and energy expenditure, and resting metabolic rate is the major component of energy expenditure, we examined whether resting metabolic rate contributes to the body-weight loss induced by rimonabant.
Materials and methods

Animals. A total of 20 male adult mongrel dogs were included in this study. Animals were housed in kennels at the vivarium of the Keck School of Medicine at the University of Southern California. This study was approved by the ethics committee of the University of Southern California.

Induction of fat accumulation. Dogs were initially maintained on a standard diet for a 3-week acclimation period (3885 kcal/d, 39.4% carbohydrates, 33.2% fat, 27.4% proteins). Food was presented from 0900–1200 h, daily. To induce fat accumulation we switched from the standard diet to a hypercaloric high-fat diet (HHFD), which consisted of 5527 kcal/d (27.7% carbohydrates, 53.0% fat, 19.3% proteins), also presented from 0900–1200 h, daily. We have previously reported that 6 weeks is an adequate period to observe significant increases in adiposity (24, 25) and body weight (23). Thus, the HHFD was maintained for a minimum of 6 weeks (9±2 wks) period prior to any drug treatment.

Rimonabant treatment. After the initial fat feeding period of, animals were randomly segregated into two groups, rimonabant (n = 11) or placebo (n = 9). Animals were matched for body weight (31.7 ± 1.3 and 31.8 ± 1.5 kg; rimonabant versus placebo group, respectively). Rimonabant (Sanofi-Aventis, Paris, France) was encapsulated (AMC Pharmacy, Burbank, CA) and administered orally at 1.25 mg · kg⁻¹ · d⁻¹, while placebo-treated animals received inert capsules. The dose was chosen based on tolerability of the drug. We used 3 criteria to assess tolerability in 5 dogs which were not included in the
current study. We measured food intake, blood pressure and gross motor movements – muscle fasciculations made by visual observations. The first dose selected was 5 mg/kg. At this dose, animals did not eat, exhibited blood pressure >160/100 mmHg and showed severe muscle fasciculations. After a washout period in which all parameters returned to normal, the dose was titrated down to 2.5 mg/kg. At 2.5 mg/kg, similar observations were made to those at 5 mg/kg dose; therefore it was decided to decrease to 1.25 mg/kg. At this dose, we observed a transient decrease in food intake and blood pressure. In addition, we did not observe evidence of muscle fasciculations. The final dose selected is 2-2.5 times higher than the efficacious 20 mg dose administered to humans. During the 16 weeks of treatment, all animals were continued on the HHFD.

**Food intake and body weight.** We performed daily recordings of food intake throughout the study as well as weekly recordings of body weight. Food intake data for each specific week are presented in the text as means of the 7-day recordings for that week.

**Abdominal trunk composition.** The amount of fat tissue and non-fat tissue in the abdominal trunk was quantified by magnetic resonance imaging (MRI) using a 1.5 T Gemsow Scanner (General Electric). The MRI scanning included 6 sessions: prior to the beginning of the HHFD (week –6), after induction of increased body weight and adiposity and prior to initiation of drug (week 0), and thereafter at weeks 2, 6, 12 and 16 weeks of treatment. For scans, dogs were pre-anesthetized with 1.35 mg of atropine sulfate plus 5 mg of acepromazine (s.c.), then anesthetized with a single i.v. dose of a mixed solution of ketamine (10 mg/kg) and diazepam (0.5 mg/kg), slowly administered.
Dogs were placed on the scanner table in supine position with the front legs flexed and the hind legs extended. The scanning consisted of 30 contiguous slices 1-cm thick (T1-weighted, repetition time = 500 ms, echo time = 14.0 ms), placing the first slice at the level of the junction between the inferior-limb and the trunk. In an attempt to get comparable repeated measurements along the study, the left renal hilum was chosen as a landmark for all sessions. The analysis of the data was based on 11 consecutive slices, 5 upper and 5 below the landmark. Body composition in the abdominal trunk was divided in 5 categories: visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), total fat (VAT + SAT), non-fat tissue and total tissue (total fat + non-fat tissue). Images were retrieved to a PC with eFILM Lite software (v. 2.0.1. and v. 2.1.2., Merge Healthcare, Milwaukee, WI, USA). Every image was analyzed using the software Scion Image for Windows (Alpha 4.0.3.2., Scion Corporation, Frederick, MD, USA) to differentiate fat from non-fat tissue based on pixel intensity as previously described (25). VAT was defined as the fat located in the intra- and retro-peritoneal region, and this region was separated from the SAT by manual trace. For each slice the area was calculated in cm$^2$ (area of 226 x 256 pixels equivalent to 34.9 x 34.9 cm$^2$) and multiplied by the thickness of the slice to obtain the volume. The total volume of each component of the trunk was obtained by summing the partial volumes from each slice.

**Resting metabolic rate.** In a subset of dogs (rimonabant, $n = 7$; placebo, $n = 5$) we assessed resting metabolic rate by indirect calorimetry. The calorimetric chamber used consisted of a standard dog kennel adapted for the experiments. All dogs were acclimated to the chamber three weeks prior to the initiation of the protocol. Dogs were fasted for at least 12 hours prior to each experiment. We assessed resting metabolic rate at weeks 0, 2,
6, 12 and 16. For each weekly session, the recordings were obtained between 0630–1030 h over a period of 2 days, randomly assigning six dogs to each day. The gas analyzer module VacuMed Vista MX (VacuMed, Venture, CA, USA) was calibrated before each experiment, which consisted of 25 min, with recordings every 30 s. Data were analyzed using TurboFit software (VacuMed) and the resting metabolic rate was calculated using the modified Weir’s equation: resting metabolic rate = 1.44*(3.9*VO₂ + 1.1*VCO₂), where VO₂ is the oxygen consumed and VCO₂, the CO₂ exhaled (45). For a given animal, we considered as an accurate value for resting metabolic rate when six consecutive measurements of the levels of CO₂ in the chamber and the resting metabolic rate where within 3% difference of each other.

**Statistical analysis.** All data were expressed as means ± SE. Comparison of means within groups were performed using the repeated measure one-way ANOVA test, with Tukey test as a post hoc analysis. Non-paired t test was used to compare means between groups. General linear model was used to determine multiple correlation (R) between variables measured repeatedly throughout the study. All the analyses were done using Statistica (StatSoft Inc., Tulsa, OK, USA). Differences were assumed to be significant if the P value was less than 0.05.
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Results

Initial induction of fat accumulation (weeks –6 to 0). The initial 6 weeks of HHFD resulted in a 7.1% increase in body weight (n = 20) from 29.6 ± 0.8 to 31.8 ± 1.0 kg (P < 0.001). These changes were accompanied by a 35.8% increase in total fat in the abdominal trunk (733.3 ± 58.5 to 995.5 ± 90.8 cm³, P < 0.001) with no changes in non-fat tissue (P = 0.166). There were increases in both VAT (28.1 %, P < 0.001) and SAT (66.8%, P < 0.001), with a predominance of SAT accumulation in absolute numbers (145.7 ± 32.0 vs. 116.6 ± 21.0 cm³, SAT and VAT, respectively) (Fig. 1). The fat percentage of the total tissue increased from 24.9% to 31.5% (P < 0.001).

Effect of rimonabant on body weight and food intake (weeks 0 to 16). By week 16 of treatment and continued HHFD, rimonabant treated dogs lost 2.8% of their body weight while placebo dogs increased their body weight by 6.5%. However, body weight was not different between groups (P = 0.156). In the rimonabant group we observed transient decreases in food intake, at week 2 (P < 0.001) and at week 16 (P = 0.027). Placebo group showed no changes in food intake throughout the study. When we normalized food intake to body weight we found a significant difference between groups only at week 2 (65.1 ± 4.1 vs. 81.2 ± 3.0 kcal · kg⁻¹ · d⁻¹, rimonabant vs. placebo, respectively; P = 0.007) (Table 1).

Effect of rimonabant on the abdominal fat composition. Fat changes in the abdominal trunk from representative dogs in each group are shown in Fig. 2. The body weight loss
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seen in the rimonabant group was consistent throughout the study, and occurred concomitant with a loss of total fat in the abdominal trunk. Interestingly, VAT remained unchanged in the rimonabant group, while SAT decreased consistently from week 6 to the end of the study. Conversely, placebo group showed a progressive increase in total fat, including VAT and SAT, reaching significant changes in the last 4 weeks of the study (Table 1). Trends of total fat, VAT and SAT changes in both groups throughout the study are shown in Fig. 3.

At the end of the study, total fat, VAT and SAT, but not non-fat tissue, expressed as percent changes of the baseline (Δ), were significantly different between groups (rimonabant versus placebo, Δ total fat: –14.0 vs. 26.2%, P < 0.001; Δ VAT: –9.8 vs. 26.7%, P = 0.004; Δ SAT: –19.5 vs. 28.8%, P < 0.001; Δ non-fat tissue: 5.9 vs. 2.6%, P = 0.303). Though absolute values of VAT and SAT seemed to be higher at week –6 in the rimonabant group, compared with placebo (Fig. 3), they were not statistically different (P = 0.101 and 0.381, for VAT and SAT, respectively). Importantly, body weight changes were associated with fat tissue and non-fat tissue changes in the rimonabant group (vs. total fat: $R^2 = 0.43$, $P = 0.001$; vs. VAT: $R^2 = 0.37$, $P = 0.001$; vs. SAT: $R^2 = 0.39$, $P < 0.001$; vs. non-fat tissue: $R^2 = 0.22$, $P = 0.041$) and in the placebo group (vs. total fat: $R^2 = 0.8$, $P < 0.001$; vs. VAT: $R^2 = 0.70$, $P < 0.001$; vs. SAT: $R^2 = 0.72$, $P < 0.001$; vs. non-fat tissue: $R^2 = 0.47$, $P < 0.001$). Hence, total fat and non-fat tissue were predictors of body weight changes in the rimonabant group.

Body weight changes are not associated with either resting metabolic rate or food intake changes. In a subset of dogs ($n = 12$) we evaluated the contribution of food intake
and resting metabolic rate to body weight changes induced by rimonabant. The dogs treated with rimonabant \((n = 7)\) lost 4.3% of their body weight \((P < 0.001)\), while the placebo dogs \((n = 5)\) increased their body weight by 5.9% \((P = 0.003)\). However, the difference between food intake by the groups was not significant (Fig. 4A). Rimonabant reduced food intake only during the first two weeks of the study (baseline: 2570.9 ± 185.5 kcal/d; week 2: 1808.4 ± 152.3 kcal/d; \(P < 0.001\)). Placebo group showed no changes on food intake at any week. When normalized to body weight, food intake was significantly less in the rimonabant group compared with the placebo group only at week 2 \((60.8 ± 5.6 \text{ vs. } 81.4 ± 4.4 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}; P = 0.022)\) (Fig. 4B).

At the end of the study, rimonabant treatment did not result in changes in resting metabolic rate (week 0: 1618.8 ± 75.9; week 16: 1414.1 ± 85.5 kcal/d; \(P = 0.264\); repeated measures ANOVA). Likewise, resting metabolic rate remained unchanged in the placebo group (week 0: 1632.9 ± 63.7; week 16: 1628.5 ± 139.9 kcal/d; \(P = 0.999\); repeated measures ANOVA). Moreover, there was no difference in resting metabolic rate between groups at any week (Fig. 4C). We found that body weight changes in the rimonabant group were not associated with either resting metabolic rate \((R^2 = 0.24; P = 0.154)\) or food intake \((R^2 = 0.24; P = 0.166)\) changes. Furthermore, in the rimonabant group, total fat, VAT and SAT changes were not associated with resting metabolic rate (vs. total fat: \(R^2 = 0.10, P = 0.660\); vs. VAT: \(R^2 = 0.08, P = 0.756\); vs. SAT: \(R^2 = 0.15, P = 0.420\)), but were associated with food intake changes (vs. total fat: \(R^2 = 0.41, P = 0.013\); vs. VAT: \(R^2 = 0.34, P = 0.044\); vs. SAT: \(R^2 = 0.38, P = 0.024\)).
Discussion

Excessive abdominal fat is a high risk factor for the development of insulin resistance and Type 2 diabetes. Clinical trials have shown a reduction in waist circumference in subjects treated with rimonabant. However, to date, direct evidence showing the effects of rimonabant on visceral and subcutaneous adipose tissue in the abdominal region has not been reported. In the present study, we induced abdominal fat accumulation in lean dogs (an animal model similar to human obesity) using a high fat hypercaloric diet. We examined the effect of rimonabant treatment on visceral and subcutaneous fat in the abdomen. We also examined the contribution of food intake and energy expenditure to body weight changes induced by rimonabant. The present study confirms previous findings, demonstrating an effect of rimonabant to reduce adiposity as well as body weight with only a transient reduction in food intake. In addition, we clearly demonstrate that rimonabant prevents additional fat accumulation in VAT depot, while significantly reducing SAT content during the maintenance of a HHFD. These changes in fat depots occurred in the absence of any changes in non-fat tissue. Thus, CB1 receptor antagonism has a profound effect to reduce the amount of stored fat in an animal model reminiscent of human obesity.

The decrease in body weight induced by rimonabant was significant after 2 weeks of treatment until the end of the study (Fig. 4A). However, the dogs exhibited only a transient decrease in food intake at week 2 (Fig. 4B). This transience in the effect of RIM on food intake has been consistently reported in rodent studies (9, 11, 35, 36). Importantly, we did not find a correlation between food intake and body weight changes.
Together, these results suggest that food intake alone cannot explain the profound effect of RIM to reduce weight.

The observation that rimonabant induced a preferential loss of SAT, rather than VAT, does not appear to be in concordance with the notion that adipocytes from VAT have a higher basal lipolytic rate than adipocytes from SAT. However, it must be noted that in the present study, fat feeding was maintained throughout the treatment period. We have recently hypothesized that fat accumulates initially in the VAT depot and then spills over into the SAT depot, known as the overflow hypothesis (2). Hence, in the presence of continued fat feeding, rimonabant may act to prevent further fat accumulation in the VAT while reducing SAT. These actions of rimonabant on adipose tissue are indicative of direct peripheral effects of rimonabant. Several *in vitro* studies support a direct effect of rimonabant on adipose tissue. The expression of CB1R has been found in both rodent (1, 6) and human (10, 32, 38) adipocytes. Interestingly, rimonabant has been shown to block the rate of lipogenesis induced by the CB1R agonist WIN-55,212 in primary adipocytes (6) and stop the accumulation of lipid droplets in cultured clonal preadipocytes (12). Whether CB1R expression is found in canine fat tissue is largely unknown. However, we have recently shown that rimonabant treatment prevents the accumulation of large adipocytes (>100 µm) in subcutaneous and omental fat in dogs fed a HHFD (17).

It has been reported that increased fat accumulation in adipocytes lead to an increase in lipolysis (47). While we found an increase in the number of large adipocytes (>75 µm) with fat feeding, we did not observe any differences in basal lipolysis measured in vitro (data not shown). These observations lead us to speculate that there is a threshold in which lipid accumulation in adipocytes must reach in order to observe changes in
lipolytic activity. Consistent with this notion is a recent report in rats that demonstrate no change in basal lipolysis in high fat fed rodents at a time when mesenteric and retroperitoneal fat pads are significantly increased (5). However, after prolonged periods of fat feeding and consequently increased fat accumulation, differences in lipolytic activity were noted. Moreover, some studies suggest that the antiobesity effects of rimonabant are due to increased lipolysis, yet we observe no differences between the two groups. The molecular mechanism as to how rimonabant prevents visceral fat accumulation and reduces subcutaneous fat content remains to be elucidated. Clearly, the roles of lipogenesis, LPL activity and re-esterification rates must be taken into account. A potential mechanism may be gleaned from mouse studies that demonstrate inhibition of lipid accumulation into adipocytes by blocking pre-adipocyte proliferation (12).

An alternative mechanism for the reduction in body adiposity and weight loss may be attributed to changes in energy expenditure. Energy expenditure has been shown to be enhanced with rimonabant treatment. Since resting metabolic rate represents the largest component of total energy expenditure (29, 37), we examined whether body weight loss induced by rimonabant was dependent on resting metabolic rate changes. In a subset of dogs we conducted a study to determine whether increases in energy expenditure could explain the body weight changes. Surprisingly we found no significant changes on resting metabolic rate during the study (Fig. 4C). Moreover, there was no association between resting metabolic rate and body weight changes. These results suggest that other components of total energy expenditure might explain the body weight loss (29) (i.e. physical activity and adaptive thermogenesis). It has been reported that rimonabant increases grooming (18) and scratching activity (18, 28) in rodents. In addition, it has
been shown that acute (28) and chronic (15) administration of rimonabant increases total energy expenditure in rats. Physical activity was not monitored in this study. However, weekly core body temperatures (data not shown) in the dogs remained invariable throughout the study, indirectly suggesting that the body heat production was not altered. Thus, the reduction of body weight may be due to changes in spontaneous physical activity.

Clinical studies aimed to determine the effect of other anti-obesity drugs in combination with a low-calorie diet on abdominal fat distribution, either by computed tomography or MRI, demonstrate a decrease in both VAT and SAT compartments. Orlistat, an inhibitor of pancreatic lipase(40) and sibutramine, a blocker of serotonin and norepinephrine reuptake, (20, 21, 48) were able to significantly reduce abdominal fat content in obese subjects. However, unlike our study, the aforementioned studies are treatment therapies in combination with a low-calorie diet. In the face of continued fat feeding, it may be difficult to see a true reduction in visceral fat, particularly if fat is preferentially deposited in this depot.

It has been reported that over-expression of adiponectin in mice resulted in expansion of SAT and was associated with an improvement of the metabolic profile (22). In addition, it has recently been reported that transplantation of SAT into the VAT depot improved insulin sensitivity in mice (41). Apparently, these results might be in conflict with the fact that the effect of rimonabant was more pronounced in SAT. Though, the findings from these studies are interesting, the extrapolation of those results to human obesity is unknown, given the differences in fat distribution and composition between humans and rodents. In fact, if SAT were beneficial, liposuction would significantly
imper the metabolic profile in humans that undergo this procedure. For example, some studies have not shown changes in metabolic parameters after 10-12 weeks of follow-up (27) or within 1-4 years of a significant sustained reduction of SAT (31). Together, these human studies suggest that SAT does not have a beneficial effect on metabolic disease.

In conclusion, this study provides the first direct evidence of the effect of rimonabant on fat distribution in the abdominal region in a canine model which parallels fat distribution in humans. Chronic treatment with rimonabant resulted in a reduction of body weight and fat content in the abdominal trunk with no changes in non-fat tissue, suggesting a direct effect of rimonabant on adipocytes. In contrast, with the significant increases of both SAT and VAT in placebo, rimonabant prevented additional VAT accumulation and decreased SAT. The reduction in overall body weight was not associated with either resting metabolic rate or food intake changes. However, an increase in spontaneous physical activity cannot be excluded as a possible mechanism to induce weight loss. These findings provide evidence of a peripheral effect of rimonabant to reduce adiposity and body weight, possibly through a direct effect on adipose tissue.
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Disclosures

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Legends for figures

**Fig. 1** Bars represent changes in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), measured by magnetic resonance imaging, in the abdominal trunk from dogs \(n = 20\) maintained exclusively on a hypercaloric high-fat diet (HHFD) for 6 weeks. White bars represent week –6 (pre-HHFD); black bars, week 0 (post-HHFD). Data are means ± SE. \(* P < 0.001\), compared with week –6.

**Fig. 2** Magnetic resonance imaging (T1-weighted) of the abdominal trunk in 3 representative dogs from each group, placebo and rimonabant, maintained on a hypercaloric high-fat diet. Images correspond to scans at the level of the left renal hilum. Placebo dogs progressively gained more fat (represented in yellow) during the high-fat diet period, while in rimonabant dogs fat accumulation was prevented. Non-fat tissue is shown in red/brown color. R: right, L: left.

**Fig. 3** Changes in total fat, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in the abdominal trunk from dogs receiving rimonabant \(n = 11\) or placebo \(n = 9\) concomitant with a hypercaloric high-fat diet (HHFD) during 16 weeks. Data are means ± SE. \(\dagger P < 0.05\), \(\dagger\dagger P < 0.01\), compared with week –6. \(* P < 0.05\), \(\dagger* P < 0.01\), \(\dagger\dagger* P < 0.001\), compared with week 0.

**Fig. 4** Effect of rimonabant on body weight, food intake and resting metabolic rate in dogs fed a hypercaloric high-fat diet (HHFD). Solid squares represent the rimonabant
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group \((n = 7)\); open triangles, placebo group \((n = 5)\). Dogs received either rimonabant or placebo from week 0 through week 16, as indicated in \((A)\), for all panels. Rimonabant dogs significantly reduced their body weight from week 2 until the end of the study \((A)\); however, food intake was reduced only at week 2 \((B)\). There were no changes in resting metabolic rate \((C)\). Dashed lines indicate in each panel the baseline reference values immediately prior to the beginning of treatment. Data are means ± SE. *\(P < 0.05\), between groups.
Table 1. Food intake, body weight and abdominal trunk composition in dogs maintained on a HHFD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 6</th>
<th>Week 12</th>
<th>Week 16</th>
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<td>Rimonabant group (n = 11)</td>
<td></td>
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<tr>
<td>FI (kcal/kg/d)</td>
<td>80.2 ± 3.7</td>
<td>65.1 ± 4.1*§</td>
<td>80.6 ± 5.0</td>
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<td>Body weight (kg)</td>
<td>31.7 ± 1.3</td>
<td>29.9 ± 1.1‡</td>
<td>30.1 ± 1.1‡</td>
<td>30.6 ± 1.2*†</td>
<td>30.8 ± 1.1†</td>
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<tr>
<td>Abdominal trunk:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT (cm³)</td>
<td>3105.6 ± 145.5</td>
<td>2953.7 ± 115.9</td>
<td>2898.9 ± 125.9†</td>
<td>3056.3 ± 123.4</td>
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<td>NFT (cm³)</td>
<td>2016.0 ± 88.0</td>
<td>2004.2 ± 75.3¶</td>
<td>2010.0 ± 71.1</td>
<td>2103.0 ± 82.1</td>
<td>2126.9 ± 85.5</td>
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<tr>
<td>TF (cm³)</td>
<td>1089.5 ± 118.3</td>
<td>949.5 ± 95.2†</td>
<td>888.9 ± 109.3¶</td>
<td>953.3 ± 93.1†</td>
<td>935.6 ± 108.2†</td>
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<td>VAT (cm³)</td>
<td>611.3 ± 57.9</td>
<td>523.6 ± 41.6</td>
<td>519.7 ± 60.0</td>
<td>574.0 ± 48.7</td>
<td>555.9 ± 63.9</td>
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<td>SAT (cm³)</td>
<td>478.3 ± 63.5</td>
<td>425.8 ± 59.1</td>
<td>369.2 ± 54.7‡</td>
<td>379.3 ± 46.9‡</td>
<td>379.7 ± 48.9‡</td>
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<td>VAT/SAT</td>
<td>1.4 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.5 ± 0.1</td>
<td>1.6 ± 0.1†</td>
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<td>TF (%) of the TT</td>
<td>34.5 ± 2.4</td>
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<td>VAT (%) of the TF</td>
<td>57.1 ± 1.4</td>
<td>56.3 ± 1.9</td>
<td>59.2 ± 1.9</td>
<td>61.0 ± 1.3†</td>
<td>59.7 ± 1.4</td>
</tr>
<tr>
<td>SAT (%) of the TF</td>
<td>42.9 ± 1.4</td>
<td>43.7 ± 1.9</td>
<td>40.8 ± 1.9</td>
<td>39.0 ± 1.3‡</td>
<td>40.3 ± 1.4</td>
</tr>
</tbody>
</table>

| Placebo group (n = 9) | | | | | |
| FI (kcal/kg/d) | 84.8 ± 4.1 | 81.2 ± 3.0 | 83.4 ± 3.6 | 80.2 ± 5.7 | 76.3 ± 4.3 |
| Body weight (kg) | 31.8 ± 1.5 | 31.8 ± 1.5 | 32.4 ± 1.5 | 33.5 ± 1.7‡ | 33.9 ± 1.9† |
| Abdominal trunk: | | | | | |
| TT (cm³) | 3113.7 ± 143.4 | 3173.4 ± 146.0 | 3220.9 ± 161.6 | 3371.8 ± 218.7† | 3404.5 ± 207.4† |
| NFT (cm³) | 2233.1 ± 106.8 | 2229.2 ± 63.9 | 2241.1 ± 91.7 | 2283.7 ± 113.2 | 2282.7 ± 99.2 |
| TF (cm³) | 880.6 ± 138.2 | 944.1 ± 138.6 | 979.8 ± 165.9 | 1088.1 ± 202.9* | 1121.8 ± 194.7‡ |
| VAT (cm³) | 506.0 ± 70.3 | 551.2 ± 76.6 | 555.9 ± 83.9 | 624.9 ± 112.4 † | 641.0 ± 103.8* |
| SAT (cm³) | 374.6 ± 74.8 | 393.0 ± 70.5 | 423.9 ± 88.3 | 463.2 ± 95.9* | 480.8 ± 97.5‡ |
| VAT/SAT | 1.5 ± 0.2 | 1.3 ± 0.2 | 1.4 ± 0.2 | 1.4 ± 0.1 | 1.4 ± 0.1 |
| TF (%) of the TT | 27.7 ± 3.2 | 28.9 ± 2.8 | 29.5 ± 3.3 | 30.9 ± 3.6* | 31.7 ± 3.4‡ |
| VAT (%) of the TF | 58.6 ± 2.8 | 58.9 ± 2.8 | 57.8 ± 2.6 | 57.8 ± 2.3 | 57.8 ± 2.6 |
| SAT (%) of the TF | 41.4 ± 2.8 | 41.1 ± 2.8 | 42.2 ± 2.6 | 42.2 ± 2.3 | 42.2 ± 2.6 |

FI, food intake; HHFD, hypercaloric high-fat diet; NFT, non-fat tissue; SAT, subcutaneous adipose tissue; TF, total fat; TT, total tissue; VAT, visceral adipose tissue. Values are means ± SE. *P < 0.01; †P < 0.05; ‡P < 0.001; compared with week 0. §P < 0.01; ¶P < 0.05; compared with placebo.