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Original Article

Comparison between cafeteria and high-fat diets in the induction of metabolic dysfunction in mice

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Abstract: This study sought to compare the metabolic responses induced by high-fat (HF) diet and cafeteria (CA) diet in mice. Adult male C57BL/6J mice were assigned into groups fed a chow (C, n=13), CA (n=12) or HF (n=11) diet during 12 weeks. Diets did not change body weight, Lee index, inguinal subcutaneous fat, the weight of organs and muscles, resting arterial pressure and heart rate. CA and HF increased visceral fat pad mass compared to C group, but only CA group showed greater adipocyte diameter and food intake compared to the C. Food intake was reduced in HF compared to C group. CA and HF showed hyperglycemia in the 3rd, 6th, 9th and 12th week and all values were higher in CA than HF, except in the 6th week. CA group showed glucose intolerance (GI) in the 6th week, while HF group did not show GI until the 9th week. CA decreased insulin sensitivity compared to C in the 12th week (kITT=3.3±0.2%/min vs. 4.2±0.1%/min). CA and HF groups presented higher insulin, leptin, total cholesterol, LDL-C, triglycerides and FFA levels compared to the C group. Total cholesterol and LDL-C in mg/dL were higher in the HF (161.9±7.2 and 57.5±13.4) than the CA (110.5±9.1 and 48.5±11.4), and HDL-C was higher in the HF than in the C and CA groups. In conclusion, the CA diet was more efficient to induce hyperphagia, adipocyte hypertrophy, hyperglycemia, earlier GI and insulin resistance, while the HF diet was more efficient to induce lipid profile changes.

Keywords: Diet, adiposity, insulin resistance, leptin, lipid profile, mice

Introduction

The prevalence and incidence of metabolic diseases such as type 2 diabetes, obesity and metabolic syndrome is increasing worldwide [1] and has contributed to the development of cardiovascular risk and mortality in the population [2, 3]. Although some of the lifestyle responsible for the development and progression of metabolic diseases are described in the literature, such as physical inactivity and the consumption of high-fat diet [4, 5], it is still necessary to better understand the pathophysiology, prevention and treatment of obesity, insulin resistance, type 2 diabetes, dyslipidemia and metabolic syndrome.

In this sense, the development of animal models with metabolic dysfunction induced by diets with high caloric densities have been widely reported in the literature, as they can be used to reproduce the etiology, course and outcomes of human metabolic diseases [6-11]. The availability of a well characterized animal model can be useful to the investigation of cellular and molecular aspects involved in the development and progression of several metabolic dysfunctions. Diets rich in sucrose, dextrose, fructose, fat or any of these combined promote important changes in carbohydrate metabolism resulting in insulin resistance and type 2 diabetes, weight gain and adiposity, dyslipidemia, and arterial hypertension in rodents [9-11]. When the palatability of the diet is improved, such as in a cafeteria diet composed of sugar, butter, peanut butter and condensed milk, the metabolic dysfunction can be exacerbated due to voluntary hyperphagia [12]. It has been shown that mice fed a cafeteria diet develop metabolic syndrome more severely than high-fat diet [13], a high-fat diet is more efficient to induce obesity [14], and a high-salt or high-fructose diet is more efficient to induce hypertension [15, 16].

Table 1. Nutritional composition of the diets

	Chow	Cafeteria	High-fat
Kcal/g	3.78	4.23	5.17
Carbohydrates	55%	56%	33.8%
Protein	22%	14.8%	26.1%
Total fat	4%	18.7%	35.5%
Fiber	6%	3.2%	0.1%

Despite the existence of several studies regarding diet-induced metabolic syndrome in other animal models, there are few data resulting from direct comparisons between different patterns of diet and metabolic dysfunction in rats [14, 17]. However, given the physiological differences between rats and mice, a knowledge gap still exists when we seek studies that have comparatively evaluated the metabolic responses of mice subjected to high-fat diet and cafeteria diet. Thus, this study aimed to compare the metabolic responses induced by high-fat diet and cafeteria diet in mice. This approach can determine the efficiency of diets to induce metabolic dysfunction in mice and can be useful to investigate preventive and therapeutic strategies in future studies.

Materials and methods

Animals

Ten-week-old male C57BL/6 mice were assigned to three groups: chow diet (C, n=13), cafeteria diet (CA, n=12) and high-fat diet (HF, n=11). Animals were maintained under the same housing conditions (12-h light/12-h dark cycle, temperature 22±2°C), with free access to tap water and food *ad libitum* during 12 weeks. All procedures were performed in accordance with the guidelines of the Brazilian College for Animal Experimentation and were approved by the Ethics Committee of the School of Physical Education and Sport of the University of Sao Paulo (#26/2009).

Diet composition

The nutritional composition of the diets is given in **Table 1**. The standard chow diet and high-fat diet used were obtained from Nuvilab (Paraná, Brazil) and Bio-serve (Frenchtown, USA), respectively. The cafeteria diet was modified from Estadella et al. [17] and prepared with milk chocolate (10 g), peanuts (10 g), cornstarch crackers (5 g), sugar (5 g) and conventional diet (15 g). The ingredients were mixed and divided into pellets, weighing approximately 10 g each. The nutritional composition of the cafeteria diet was evaluated in accordance with the Manual of Procedures and Determinations General of the Adolfo Lutz Institute [18].

Food intake and body weight

The 24-h food intake was determined weekly throughout the study in mice that were group-housed (4 animals per cage). Body weight was measured weekly at the same time of day using a digital balance (Gehaka, Model BK4001, Brazil). Body weight gain was calculated as the difference between body weight measured at the beginning and at the end of the experimental protocol.

Glucose tolerance test (GTT) and insulin tolerance test (ITT)

The analyses of fasting glucose (12-h) were performed before the experimental protocol, then again in the 3rd, 6th, 9th and 12th weeks. GTT and ITT were performed in awake animals at 08:00 a.m. and after a 12-h fast. The glucose load (2 g/kg body weight) was injected as a bolus intraperitoneally, and the blood glucose levels were determined in caudal blood sampled at 0, 15, 30, 60, 90 and 120 min after glucose infusion. The glucose concentration was determined using a glucometer (AccuChek Advantage Roche Diagnostics®) in the 6th, 9th and 12th weeks.

The insulin load (0.75 U/kg body weight) was injected as a bolus intraperitoneally, and the blood glucose levels were determined in caudal blood samples collected at 0, 5, 10, 15, 20, 25 and 30 min after injection. The values obtained between 5 and 30 min were used to calculate the rate constant for the disappearance of plasma glucose (kITT) by analyzing the decay curve according to the method proposed by Bonora et al. [19]. The ITT was performed after 72 h of the GTT test in the 6th and 12th weeks.

Resting arterial pressure and heart rate measurements

In a subgroup of mice randomly selected (N, n=8; CA, n=7; HF, n=7), tail-cuff arterial blood pressure and heart rate, estimated from the pulse rate, were determined via the use of a

Table 2. Body weight composition and 24-h food intake

Weights and measures	Chow (n=13)	Cafeteria (n=12)	High-fat (n=11)
Initial body weight (g)	21.2±0.7	23.3±0.6	21.4±0.5
Final body weight (g)	29.3±1.2	30.8±1.0	28.6±0.5
Body weight gain (g)	8.0±0.7	7.4±0.6	7.2±0.7
Lee Index (g/cm^3)	32.7±0.6	32.9±0.5	32.8±0.4
Periepididymal fat pad (mg/g)	12.0±1.1	18.8±3.4*	24.4±4.1*
Retroperitoneal fat pad (mg/g)	3.0±0.6	6.8±2.0*	9.5±2.0*
Subcutaneous fat pad (mg/g)	10.4±0.6	12.9±2.0	12.3±2.0
Adipocyte diameter (μm)	50.1±2.3	62.6±1.9*	55.6±2.2
Soleus muscle (mg/g)	0.54±0.1	0.61±0.1	0.53±0.1
Gastrocnemius muscle (mg/g)	7.68±1.0	6.72±0.7	6.91±0.7
Plantaris muscle (mg/g)	0.59±0.1	0.49±0.1	0.55±0.1
Kidneys (mg/g)	9.9±0.5	8.6±0.4	8.4±0.2
Lungs (mg/g)	6.2±0.3	5.8±0.5	5.8±0.3
Liver (mg/g)	40.9±1.1	36.8±0.7	37.5±2.9
Heart (mg/g)	4.5±0.2	3.6±0.3	3.7±0.1
Spleen (mg/g)	4.0±0.7	5.6±0.2	3.1±0.2
Food intake (g/animal/24-h)	2.77±0.1	3.67±0.1*,#	1.69±0.1*

Values are presented as mean ± SE. *p<0.05 *vs.* C, #p<0.05 *vs.* HF.

computerized tail-cuff system (BP 2000 Visitech Systems). Mice were acclimatized to the apparatus during daily sessions for 5 days, 1 week before the measurement. The values for each animal were determined by averaging 20 measurements obtained during their dark cycle.

Serum and tissue collection

The animals were subjected to 8-h of fasting and then killed with an intraperitoneal injection of pentobarbital sodium (4 mg/100 g body weight). The tissues were harvested and the Lee index was determined based on the naso-anal length and body weight measurements ($\sqrt[3]{}$body weight/naso-anal length) [20]. Subcutaneous (inguinal) and visceral (periepididymal and retroperitoneal) fat pads, organs and skeletal muscle were harvested and weighed. The cava venous blood was collected and centrifuged at 4°C (10.000 g for 10 min) and serum was stored at -80°C.

Insulin and leptin were quantified using mouse-specific radioimmunoassay (RIA) kits (Linco Research, Inc.). The insulin detection sensitivity was 0.02 ng/mL, the within-run variation was less than 5.8%, and the interassay CV was less than 10%. Assays were performed in duplicate using a sample volume of 50 μL. The leptin detection sensitivity was 0.2 ng/mL, the within-run variation was less than 4.6% and the interassay CV was less than 10%. Assays were performed in duplicate with a sample volume of 50 μL. Serum triglycerides, total cholesterol and HDL-c were evaluated by enzymatic colorimetric assay using commercial kits (Labtest®, Minas Gerais, Brazil). The concentrations of VLD-c and LDL-c were calculated using the Friedewald equation. Serum free fatty acids (FFA) levels were measured by colorimetric method using an FFA quantification kit (Abcam®, Cambridge, MA, USA) following the manufacturers' instructions.

Adipocyte diameter

Dissected retroperitoneal fat pads were covered in Paraplast® (Structure Probe, Inc., West Chester, PA, USA), cut on the microtome and then stained with hematoxylin and eosin. The diameter of 50 adipocytes per animal was measured in a computerized morphometric analysis system (Leica Quantimet 500, Cambridge, UK).

Statistical analysis

Data are reported as mean ± SE. The results were analyzed using one-way analyses of variance (ANOVA). The Bonferroni *post hoc* test was used to determine differences between means when a significant change was observed using ANOVA. A *p* value equal to or less than 0.05 was considered to be statistically significant (StatSoft®, Statistica v.10).

Results

Body weight and food consumption

As shown in **Table 2**, no differences were observed in body weight in the beginning and at the end of the experimental protocol. In addition, the body weight gain and Lee index were not different among groups, but both CA and HF groups showed substantial increase in the weight of retroperitoneal and periepididymal fat pads compared to the C group (p<0.05).

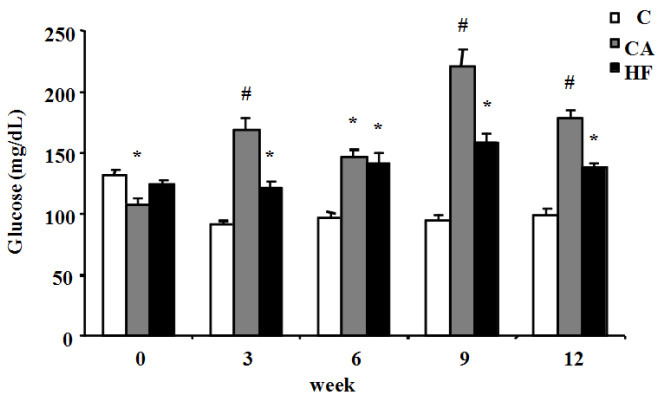

Figure 1. Fasting glycemia measured at weeks 0, 3, 6, 9 and 12 of the experimental protocol. Error bars indicate the SE. C, chow diet (n=5); CA, cafeteria diet (n=5); HF, high-fat diet (n=5). *p<0.05 *vs.* C, #p<0.05 *vs.* C and HF.

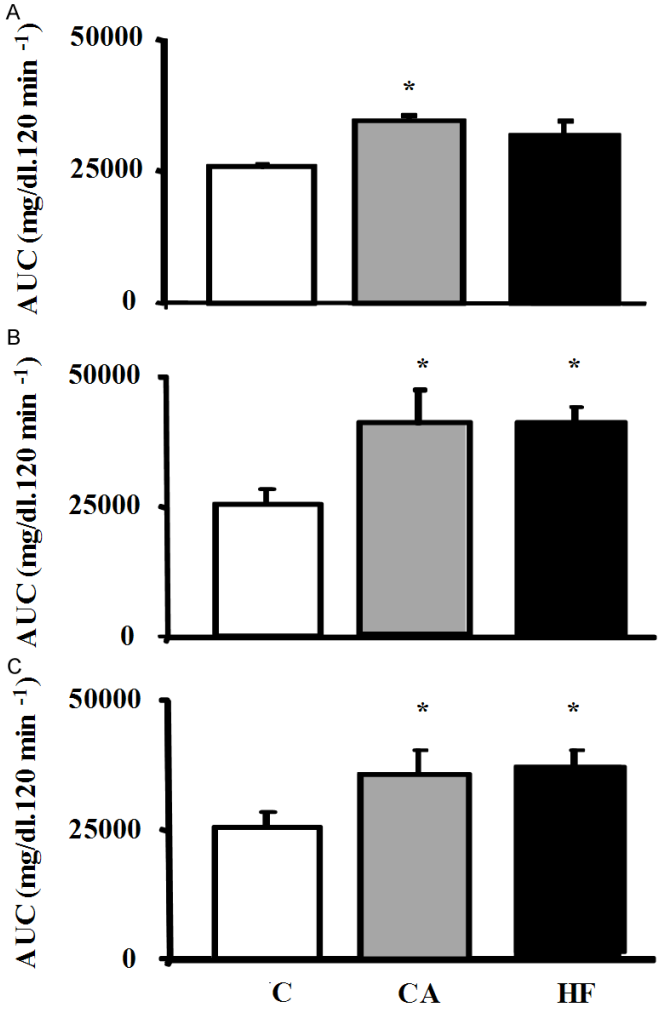

Figure 2. Area under the curve (AUC) resulting from GTT at weeks 6 (A), 9 (B) and 12 (C) of the experimental protocol. Error bars indicate the SE. C, chow diet (n=5); CA, cafeteria diet (n=5); HF, high-fat diet (n=5). *p<0.05 *vs.* C.

However, inguinal subcutaneous fat pad weights, and the weights of the soleus, gastrocnemius and plantaris muscles, kidneys, lungs, liver, heart and spleen did not differ among groups. Furthermore, the CA group showed a greater adipocyte diameter compared to the C group (p<0.05). The food intake assessed over a period of 24-h was significantly higher in the CA group compared to the C and HF groups, but the HF group showed lower food intake compared to the C group (p<0.05) (**Table 2**).

Blood analyses

At the beginning of the protocol (week 0), the CA group showed a lower fasting glucose than the C group (p<0.05) (**Figure 1**). In the 3rd, 9th and 12th weeks, the CA and HF groups had higher fasting glucose concentrations compared to the C group (p<0.05), and the fasting blood glucose of the CA group was significantly higher than the HF group (p<0.05). There was no statistical difference in fasting glucose between the HF and CA groups in the 6th week, however, the CA and HF groups maintained higher glycemia compared to the C group (p<0.05).

As shown in **Figure 2**, the CA group showed higher area under curve (AUC) compared to the C group in the 6th week of the experimental protocol (p<0.05). In the 9th and 12th weeks, the CA and HF groups showed higher AUC compared to the C group (p<0.05). The kITT did not change in the 6th week among groups, however it was significantly reduced in CA-fed mice (3.3±0.1%/min) compared to the C group (4.1±0.3%/min) in the 12th week (**Figure 3**).

As described in **Table 3**, the CA and HF groups had higher insulin and leptin levels compared to the C group (p<0.05). In addition, the CA and HF groups showed higher total cholesterol, LDL-C, triglycerides and FFA compared to the C group (p<0.05). The HF group increased HDL-C compared to C and CA groups (p<0.05), and increased total choles-

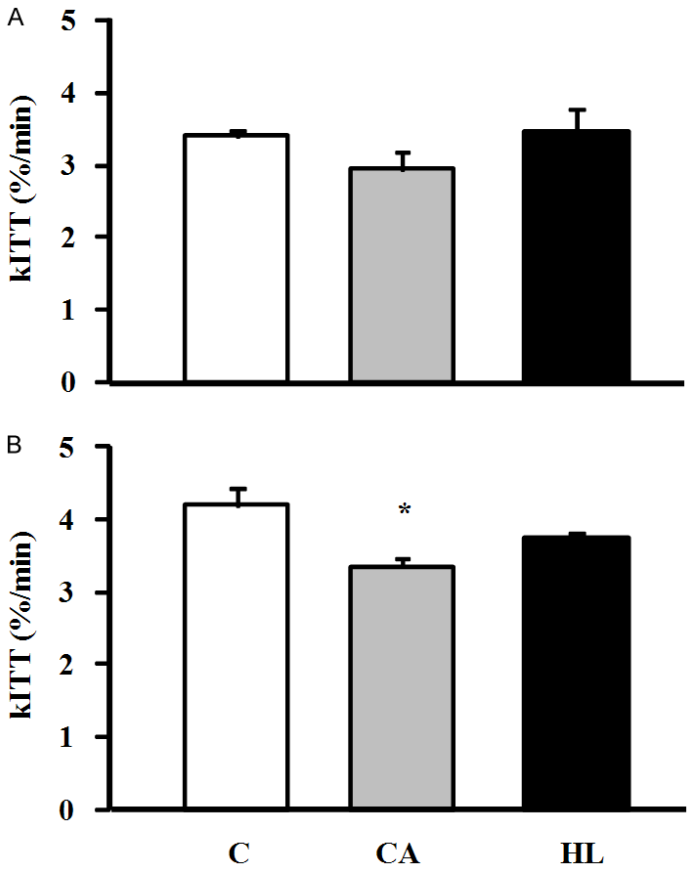

Figure 3. kITT resulting from ITT at weeks 6 (A) and 12 (B) of the experimental protocol. Error bars indicate the SE. C, chow diet (n=5-7); CA, cafeteria diet (n=5-7); HF, high-fat diet (n=5-7). *p<0.05 *vs.* C.

Table 3. Serum and lipid profile

	Chow (n=5-7)	Cafeteria (n=5-7)	High-fat (n=5-7)
Insulin (ng/ml)	0.40±0.1	0.90±0.2*	0.76±0.3*
Leptin (ng/ml)	4.3±1.2	18.3±7.3*	15.2±5.4*
Total cholesterol (mg/dL)	83.2±5.0	110.5±9.1*	161.9±7.2*,#
LDL-c (mg/dL)	18.6±6.1	48.5±11.4*	57.5±13.4*,#
HDL-c (mg/dL)	44±3.8	32.4±5.5	74.3±6.7*,#
VLDL-c (mg/dL)	22.9±1.7	29.5±2.7	30.1±2.9
Triglycerides (mg/dL)	114.7±8.7	147.4±13.5*	150.4±14.4*
Free fatty acids (mM)	0.13±0.02	0.24±0.02*	0.32±0.03*

Values are presented as mean ± SE. *p<0.05 *vs.* C, #p<0.05 *vs.* CA.

terol and LDL-C compared to the CA group (p<0.05).

Resting arterial pressure and heart rate

The baseline arterial pressure remained unchanged among groups (C=95±4.2 mmHg; CA=105±2.2 mmHg; HF=103±4.3 mmHg). In addition, resting heart rate did not differ among groups (C=620±10.7 bpm; CA=639±11.4 bpm; HF=626±7.6 bpm).

Discussion

This study reports that CA and HF diets efficiently increase visceral fat mass, induce insulin resistance and promote alterations in lipid profile in mice. These results provide evidence that both diets robustly induce metabolic dysfunction in mice but the magnitude of these responses is related to the composition of the diet.

The body weight of CA and HF groups did not differ from C group corroborating previously published studies [10, 21]. In contrast, some studies have shown weight gain induced by hypercaloric diets [9, 14, 17]. Considering that the body weight is determined by the balance between food intake and energy expenditure, the body weight observed in the HF group can be associated with the reduction of food intake. On the other hand, despite we did not measure, the increase in food consumption showed by CA group did not change body weight possible due to an increase in resting energy expenditure. This compensatory response is typically observed in mice submitted to the consumption of hypercaloric diet [22], however additional studies are necessary to confirm this response. Other factors beyond the metabolic compensation can generally explain the contradictory results of body weight observed in the literature. For example, the composition of the diets and the background of animals can influence the body weight response. Kim et al. [8] observed body weight gain in mice fed a hypercaloric diet for 12 weeks, but the lipid content was higher than used in our diet. Moreover, C57BL6/J animals are obtained by crossing C57BL/6ByJ mice, which are susceptible to diet-induced obesity and BALB/cByJ, which are resistant to diet-

induced obesity, and this may result in a heterogeneous strain for adaptation of body weight [23, 24].

Although the body weight of all mice remained unchanged, we observed that visceral fat mass increased significantly in the CA and HF groups, confirming that the diets were effective to induce obesity in mice. Moreover, the adipocyte diameter was increased in CA compared to the C and HF groups. There is considerable evidence indicating that the excessive accumulation of white adipose tissue is strongly correlated with the development of insulin resistance and type 2 diabetes [25, 26] especially due to changes in the endocrine activity, such as increases in the secretion of leptin [27] and proinflammatory cytokines [8]. In fact, our results showed that the CA and HF groups showed increased leptin secretion.

The cafeteria diet is more similar to the Western diet, especially foods with high palatability and energy density [13]. In our study, the HF mice reduced their food intake in grams while the CA group increased intake, confirming previous finding that cafeteria diet induces signs of compulsive food taking such as the inability to adapt intake behavior during periods of limited or continuous food intake [12, 13]. Moreover, considering that leptin induces appetite inhibition, the hyperphagic behavior demonstrated by the CA group may be a strong indicator of leptin resistance, which is typically associated with obesity.

The metabolism of glucose was impaired in CA and HF groups because they showed hyperglycemia, glucose intolerance and hyperinsulinemia compared to the C group. However, only the CA group showed insulin resistance, and in this group the hyperglycemia was more robust in the 3rd, 9th and 12th weeks of the diet compared to HF group. Moreover, the development of glucose intolerance in the CA group was earlier than the HF group (6th vs. 9th week of diet). These responses may be associated with the increased content of carbohydrate and high glycemic index of the CA diet, which can increase insulin secretion and induce impairment of glucose uptake. Together, the results of hyperglycemia, hyperinsulinemia and decreased insulin sensitivity showed by the CA group indicate that the cafeteria diet more efficiently to induce insulin resistance than high-fat diet in mice.

In the present study, both CA and HF groups showed increases in total cholesterol, LDL-C, triglycerides and FFA corroborating other studies [14, 28]. VLDL-C did not differ among groups, but the lipid profile changes were more robust in the HF group, which were fed a diet with more fat than the CA diet (35.5% *vs.* 18.7%). In fact, we observed that the HF group had higher total cholesterol not only due to the increased LDL-C but also due to the improvement in HDL-C. Despite the high amount of monounsaturated fatty acids in peanuts, we did not observe difference in the HDL-C in the CA group.

In the present study we did not observe changes in arterial pressure or heart rate. Despite the evidence diet-induced obesity has been associated with increases in the sympathetic nervous activity, which can induce arterial pressure and heart rate elevations [29, 30], these findings are contradictory in the literature. Calligaris et al. [11] did not observe changes in arterial pressure in mice fed a high-fat diet during 8 and 16 months, and this response could be explained by a deficiency in vasoconstriction resistance and the activation of the sympathetic nervous system secondary to insulin resistance [31]. Moreover, differences in the time of administration, species studied and the composition of diets should be considered.

In conclusion, our findings provide evidences that CA and HF diets were effective for the development of metabolic dysfunction in mice which are symptoms of metabolic syndrome, but CA more robustly induces adipocyte hypertrophy, hyperphagia, hyperglycaemia, earlier GI and insulin resistance, while HF is more robust to induce lipid profile changes.

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