Neurochemical Research (2019) 44:1869–1877
https://doi.org/10.1007/s11064-019-02821-5

ORIGINAL PAPER

Food Selection of Cafeteria Diet Affects Memory Dysfunction Related to Obesity

Grace dos Santos Feijó[1] · Simone de Oliveira[2] · Rutiane Thoen[3] · Ester Elena Schaab[4] · Ana Carolina de Moura[1] · Felipe Franco[4] · Márcia Giovenardi[1,2] · Marilene Porawski[1,2,3] · Renata Padilha Guedes[1,2]

Received: 21 March 2019 / Revised: 14 May 2019 / Accepted: 27 May 2019 / Published online: 3 June 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Cafeteria diet (CAF) mimics human Western diet and has been used in animal models to study obesity. The purpose of this study is to demonstrate that our CAF model induces metabolic disorder related to obesity and affects recognition memory in Wistar rats. We also compared the intake of two different soft drinks, as part of the CAF, on recognition memory. Our results demonstrate that CAF-fed rats increased weight gain and visceral adiposity, and exhibited hyperglycemia, hypertriglyceridemia, high leptin and low insulin plasma levels. Moreover, CAF animals showed higher lipid peroxidation in the liver and developed non-alcoholic fatty liver disease. Surprisingly, the group fed with cola-based soft drinks presented an improvement in recognition memory, whereas animals fed with orange-based soft drinks showed worse performance in this task. Our data indicates that CAF induces obesity and affects recognition memory, but the composition of the diet interfere when the neurological function is evaluated.

Keywords Diet-induced obesity · Object recognition test · Cola-based soft drink · Metabolic dysfunction · Oxidative stress · Non-alcoholic fatty liver disease

Introduction

Obesity prevalence has increased worldwide at an alarming rate. This metabolic disorder is deeply associated with conditions such as insulin resistance, diabetes, hepatic steatosis, and chronic low-grade inflammation, as well as with neurodegenerative diseases such as Alzheimer and Parkinson [1–3]. In the central nervous system (CNS), obesity-induced neuroinflammation is characterized by the activation of glial cells (microglia and astrocytes) and it can affect different CNS functions [2]. In addition, the blood brain barrier (BBB) is altered, causing an increase in its permeability that can facilitate the entry of peripheral immune cells such as lymphocytes enhancing neuroinflammation [2, 4]. The hypothalamus is a brain region involved in body weight regulation and energy balance and there is strong evidence of neuroinflammation driven by obesity in this region. However, other structures, like the hippocampus, which is crucial for learning and memory, are also affected [2, 4, 5]. The susceptibility of different brain regions can explain the worst cognitive performance, memory decline and high predisposition to neurodegenerative diseases found in obese individuals [3, 6].

Thus, obesity is a major challenge for basic science and clinical research, and different scientific models have been created trying to mimic human obesity to better understand this disease and to develop new treatment possibilities. There is a range of commonly utilized animal models of obesity. In rodents, we can highlight transgenic animals, chemical and diet-induced models of obesity [7].

Cafeteria diet (CAF) has been widely used as a diet-induced obesity model due to its capacity to cause metabolic

✉ Renata Padilha Guedes
renata.guedes@ufcspa.edu.br

1 Programa de Pós-Graduação Em Biociências, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Rua Sarmento Leite, 245, Porto Alegre, Brazil

2 Programa de Pós-Graduação Em Ciências da Saúde, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Rua Sarmento Leite, 245, Porto Alegre, Brazil

3 Programa de Pós-Graduação Em Medicina: Hepatologia, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Rua Sarmento Leite, 245, Porto Alegre, Brazil

4 Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Rua Sarmento Leite, 245, Porto Alegre, Brazil

dysfunction and related disorders, including a significant shift on gut microbiota and decrease of its diversity [8]. To simulate the Western diet, CAF has a variety of highly palatable energy-dense foods commonly used in human diet that contain substantial amounts of salt, sugar and fat. However, there is no consensus about the components of the CAF, and we can find a diversity of food combinations in the literature, which challenges the comparison of data obtained from this diet-induced obesity model [9].

In the past few decades, the use of high sugar beverages, such as soft drinks, has increased significantly [10]. Among the commonly consumed sweet beverages, we can highlight cola-based soft drinks that are also a source of other substances like caffeine. Caffeine is a psychoactive and its use is correlated with a variety of risks and benefits. Low to moderate doses of caffeine has been associated with alertness, vigilance and attention. On the other hand, high doses of caffeine increase tension and symptoms of anxiety. Regarding memory, the results are still controversial [11].

In the present study, we aimed to demonstrate the CAF ability to induce obesity and its associated metabolic and cognitive dysfunctions. Since there is no consensus about the effects of soft drinks on memory, we also sought to elucidate the effects of differential composition of CAF, by using two different soft drinks (a cola-based vs. an orange-based soft drink) on the long-term recognition memory of Wistar rats.

Materials and Methods

Animals

Male Wistar rats from the animal facility of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) were used. Animals had free access to standard rat chow and water until the age of 3 months. They were kept in plastic cages (2–3 rats per cage) under controlled temperature (22–24 °C) and light (12 h light/12 h dark cycle) conditions.

All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments, which were performed in accordance with the international laws for the care of laboratory animals, following the 3Rs guidelines. All procedures were approved by the Institutional Animal Care and Use Committee (UFCSPA, Brazil, protocol No.536/17).

Diet and Experimental Groups

Three months-old rats were randomly divided into two experimental groups: Control diet (CT, n = 16) and cafeteria diet (CAF, n = 20). After that, only for the object recognition (OR) test, a third group was added to the study. This group also received the cafeteria diet, however the soft drink offered was different. Thus, animals tested in the OR received: cafeteria diet + cola-based soft drink (n = 10), or cafeteria diet + orange-based soft drink (n = 10). The special diets for the groups CT, and CAF-cola or CAF-orange soft drinks, were administered for 16 weeks. After that, only animals from CT and CAF-cola were euthanized to collect the tissues used in all further assays.

CT group was fed with Nuvilab® CR-1 standard rat chow (Nuvital®, Curitiba, PR, Brazil) providing a total energy content of 3.4 kcal/g (63% carbohydrates, 26% protein, 11% fat). Animals from CAF group were fed, besides the standard chow, with eight palatable human food items with high energy content (Table 1): Salty snacks (Pastelina®), cake, potato chips (Ruffles®), biscuits (Tortinhas®, Isabela), cream wafer (Wafer Strawberry®, Isabela), sausage (Alibem®), mortadella (Perdigão®) and chocolate (Top®). CAF-fed rats also had free access to standard rat chow (Nuvital®, Curitiba, PR, Brazil), a soft drink (cola-based soft drink (Coca-Cola®) or orange-based soft drink (Fanta Orange®) and water ad libitum. On average, total CAF energy content included 47,5% carbohydrates, 13,5%

Table 1 Composition of CAF and energy content

	Serving size	Calories (kcal)	Total carbohydrate (g)	Protein	Total fat
Cake	60 g	221	34	3.6	8.3
Salty snacks	25 g	129	13	1.6	8
Biscuits	30 g	152	20	2	7.1
Potato chips	25 g	141	12	1.6	9.7
Cream wafer	30 g	162	19	1	9.1
Sausage	50 g	120	3	6	9.5
Mortadella	40 g	113	2.4	4.8	9.4
Chocolate	25 g	137	15	0.9	8.4
Orange-soft drink	200 ml	99	24	0	0
Cola-soft drink	200 ml	85	21	0	0

protein and 39% fat, providing a total energy content of around 4.4 kcal/g, plus 0.45 kcal/ml of soft-drink. Every day, a variety of two high-energy content items, one sweat and one salty, were mixed together and was provided in excess quantities, items were changed daily to maintain novelty (Table 2). CAF rats were fed immediately before the beginning of the dark period. The leftovers of each food item were weighed daily to determine food intake per cage. The animals were weighed in the beginning of the experiment and every week to determine weight gain.

Object Recognition Test

In the last week of diet administration, animals were submitted to the object recognition test. The test was composed of three phases divided in 3 days. On the first day, rats were habituated in an acrylic box (40 cm × 40 cm × 20 cm) containing only shavings. Twenty-four hours after habituation, the training session was conducted. Animals were placed individually in the left rear quadrant of the box containing two objects (A and B), and were allowed to freely explore them for 5 min. The long-term memory retention test was performed twenty-four hours after the training session. For the test, each rat was reintroduced into the box where one of the objects presented during training was replaced by a new object (C). The exploration time of the familiar and new object was measured. Exploration of an object was defined as directing the nose towards the object at a distance < 2 cm and/or when the animal touched the object with its nose [12]. Finally, the recognition index (RI) was calculated.

$$\mathrm{RI} = \frac{\text{Time spent exploring the new object (C)}}{\text{Time exploring the familiar object (A)} + \text{time exploring the new object (C)}}$$

Tissue and Blood Collection

After 16 weeks of diet, animals from the groups CT and CAF-cola were anesthetized with ketamine (100 mg/kg, intraperitoneal) and xylazine (10 mg/kg, intraperitoneal), the retro-orbital sinus blood was collected and the rats were euthanized for tissue collection. The serum was obtained after blood centrifugation (2500 RPM for 10 min at 4 °C) and stored at − 20 °C for later analysis. The liver and visceral fat were quickly removed and weighted. The right upper lobe was used for histology and the remaining liver was frozen for oxidative stress analyses.

Table 2 Diet options

	Diet composition
Diet 1	Chow + salty snacks + cake + soft-drink + water
Diet 2	Chow + potato chips + biscuits + soft-drink + water
Diet 3	Chow + cream wafer + sausage + soft-drink + water
Diet 4	Chow + chocolate + mortadella + soft-drink + water

Items were weighted before and after consume to calculate the food intake per cage. Items were mixed together and offered ad libitum

Blood Analyses

To analyze serum levels of insulin and leptin, a commercial kit (Millipore, USA) of an enzyme-linked immunosorbent assay (ELISA) was used following the manufacturer's instructions. Serum levels of glucose, triglycerides and cholesterol were also analyzed using colorimetric kits (Labtest, Brazil), according to the manufacturer's instructions.

Analyses of Oxidative Stress

To evaluate oxidative stress in the liver, the thiobarbituric acid reactive substances (TBARS) method was used. This assay quantifies low molecular weight compounds, predominantly malondialdehyde (MDA), which complex with thiobarbituric acid (TBA). The amount of aldehyde products generated by lipid peroxidation was quantified by the TBA reaction, using 3 mg of protein/sample added to 1 mL of thiobarbituric acid (0.67%) dissolved in 0.026 M Tris–HC1 buffer (pH 7.0). The absorbance of the supernatant was determined at 535 nm using a spectrophotometer (SpectraMax M2e Microplate Reader, Molecular Devices, MDS Analytical Technologies, USA). The results were expressed as nmol of malondialdehyde (MD) per milligrams of protein [13]. The protein concentrations in homogenates were quantified using the Bradford method [14]. We also used the Superoxide Dismutase Assay Kit (Cayman Chemical, USA) in order to determine superoxide dismutase (SOD) activity. SOD activity is represented by U/mL (one unit is defined as the amount of enzyme needed to exhibit 50% dismutation of the superoxide radical).

Histological Analyses

Liver tissues were fixed in Bouin's solution and embedded in paraffin. Serial sections of 3 µm were obtained and stained in hematoxylin–eosin. Slides were analyzed using a light microscopy (× 200 magnification) by two pathologists which were blinded to experimental design. Evaluation was performed based on the score system described by Kleiner et al. which considers the presence of steatosis (< 5% = 0; 5–33% = 1; 33–66% = 2; > 66% = 3), cellular

ballooning (none = 0; few balloon cells = 1; many cells/prominent ballooning = 2) and lobular inflammatory infiltrate (none = 0; < 2 infiltrates = 1; 2–4 infiltrates = 2; > 4 infiltrates = 3) [15].

Statistical Analyses

Data were expressed as mean ± SEM and analyzed by Student's t test. GraphPad Prism 5.0 was used for the statistical analyses. The significance level was set at $p < 0.05$.

Results

Both CAF groups ingested 27% more kcal than the CT group, irrespective they received cola or orange-based soft drinks. Each rat drank, on average, 47 mL of cola soft drink, and the group that received orange beverage had on average 58 mL daily (data not shown).

Animals from CAF group showed a higher weight gain than CT animals (t = 2.971, df = 15, p = 0.009, Fig. 1a). The amount of visceral adipose tissue was also higher in CAF-fed animals (t = 3.137, df = 18, p = 0.005, Fig. 1b). As shown in Fig. 2, CAF induced hyperglycemia (t = 3.008, df = 12, p = 0.01, Fig. 2a) and hypertriglyceridemia (t = 2.291, df = 11, p = 0.04, Fig. 2b). Metabolic features of obesity were also noticed by the increase in leptin levels in the CAF group (t = 2.366, df = 10, p = 0.03, Fig. 2d). However, insulin plasma levels were lower following CAF in comparison to CT group (t = 3.002, df = 12, p = 0.01, Fig. 2c), which may indicate deterioration of the pancreatic function caused by obesity. Altogether, these results confirm the development of obesity in CAF-fed rats.

Oxidative stress parameters were evaluated in the liver, since it is an important metabolic organ (Fig. 3). We found an increase in malondialdehyde formation, which is a marker of lipid peroxidation, in CAF-fed rats (t = 2.730, df = 10, p = 0.02, Fig. 3a). On the other hand, SOD activity was similar between CT and CAF-fed animals (t = 0.4754, df = 11, p = 0.64, Fig. 3b). Thus, CAF induced an increase in lipid peroxidation but the antioxidant defenses did not counteract the oxidative stress. These findings reinforce that obesogenic diet leads to an imbalance in oxidative status in the liver.

Pathological analyses of liver tissue showed intense hepatocyte steatosis (score = 3) and cellular ballooning (score = 2) following CAF as presented in Fig. 4. No inflammatory infiltrate was seen in the liver sections. These findings are compatible with non-alcoholic fatty liver disease (NAFLD) and a high susceptibility to the development of non-alcoholic steatohepatitis (NASH).

The object recognition test was chosen to assess long-term memory. Surprisingly, we found a higher recognition index in CAF group (t = 2.861, df = 11, p = 0.01, Fig. 5a) that received cola-based soft drink, showing that CAF + cola-based soft drink improved recognition memory. In a different cohort of rats, the soft drink offered to the animals was replaced by an orange-based soft drink. In this group, the results were the opposite, CAF-fed animals showed impairment in the recognition memory (t = 2.783, df = 18, p = 0.01, Fig. 5b).

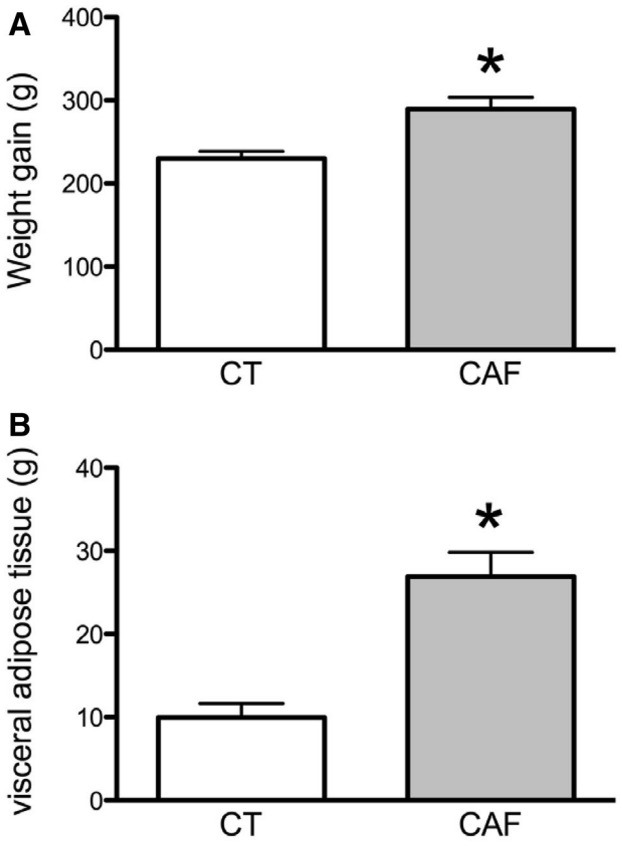

Fig. 1 Effects of CAF on weight gain and visceral adipose tissue. **a** CAF-fed rats presented significantly higher weight gain when compared with control group. **b** The total weight of visceral adipose tissue is increased in CAF-fed rats when compared with control group. Data are expressed as mean ± SEM. CAF, cafeteria diet + cola-based soft drink (n = 20); CT, control diet (n = 16); *p < 0.05

Discussion

Obesity is a public health issue characterized by a low-grade inflammation that affects numerous tissues and leads to higher risks of developing disorders such as insulin resistance, hyperlipidemia, non-alcoholic fatty liver diseases, hypertension, cardiovascular dysfunction, as well as neurodegenerative disorders [1, 3]. The increased prevalence of obesity is related to lifestyle changes, including the consumption of hypercaloric diets rich in fats and carbohydrates. To study the effects of this dietary pattern on health,

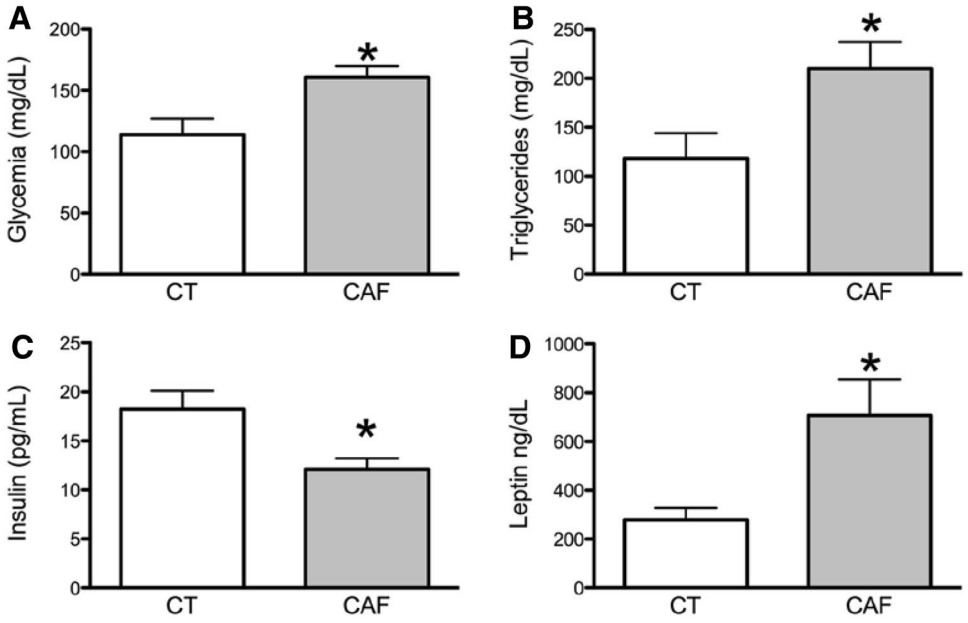

Fig. 2 Metabolic profile following 16 weeks of CAF. **a** Glycemia is increased in CAF-fed rats. **b** Triglycerides levels are significantly higher in CAF when compared with control group. **c** CAF group present reduced insulin plasma levels. **d** CAF-group presented increased leptin plasma levels. Data are expressed as mean ± SEM. *CAF* cafeteria diet + cola-based soft drink (n = 20); *CT* control diet (n = 16); *p < 0.05

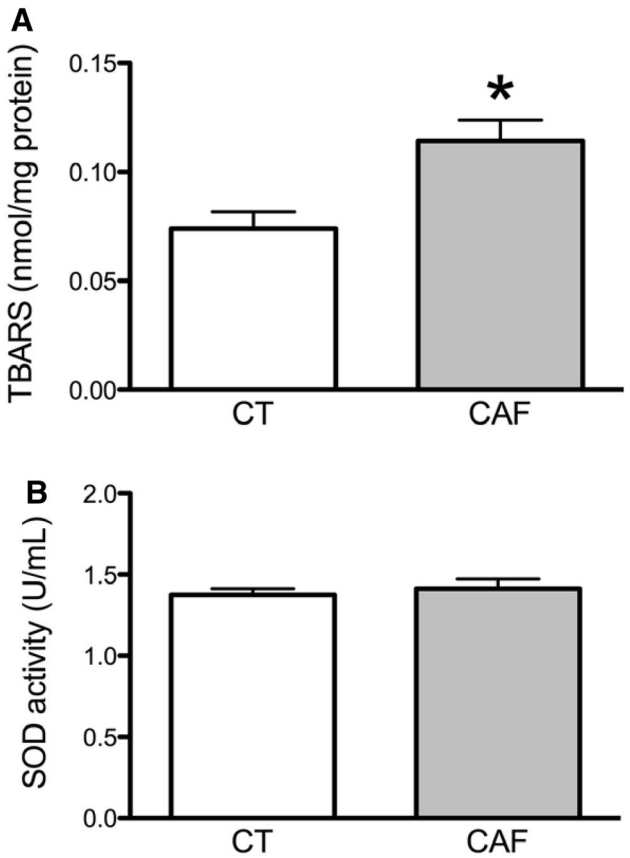

Fig. 3 Liver oxidative stress markers following CAF. **a** CAF-group showed an increase in TBARS, which indicates lipid peroxidation in the liver of obese rats. **a** Superoxide dismutase activity did not change between CT and CAF groups. Data are expressed as mean ± SEM.*CAF* cafeteria diet + cola-based soft drink (n = 20); *CT* control diet (n = 16); *SOD* superoxide dismutase, *TBARS* thiobarbituric acid reactive substances; *p < 0.05

the administration of CAF is a consolidated experimental model, representing the food intake of modern societies capable of induce obesity, glucose intolerance and inflammation in rats [16]. Here, we have demonstrated that our CAF model is effective in inducing obesity and metabolic dysfunction. We have also showed the impact of CAF on cognitive function of the rats. Furthermore, it is worth to mention the cognitive outcome was different depending on the soft drink used in CAF diet, as seen by the object recognition test.

It is well established that a dietary pattern rich in saturated fat and sugar cause detrimental effects on the brain and cognitive function [3]. Even before the development of metabolic syndrome, male rats fed with CAF have shown worst cognitive performance than control group [17]. Also, there is evidence that obesity causes an increase in adipocyte-secreted inflammatory cytokines. This inflammatory state will lead to an impairment of the cognitive behavior, and, thereby, triggers the process of dementia [6].

Despite the role of the hypothalamus in the body weight regulation and energy balance, the neuroinflammation derived from obesity is not restricted to this area [2]. Indeed, diet-induced obesity leads to an increase in BBB permeability in the hippocampus, while both prefrontal cortex and striatal BBB are unaffected [4]. The hippocampus is a crucial brain area for learning and memory, and it is highly susceptible to dietary insults [2, 5]. For instance, after only 10 days of exposure to Western diet, there was a decrease in the hippocampal GLUT1 that supports glucose transport into the CNS and this was associated with learning and memory deficits [18].

Different mechanisms were identified as being able to alter cognitive function in obesity, including reduced levels

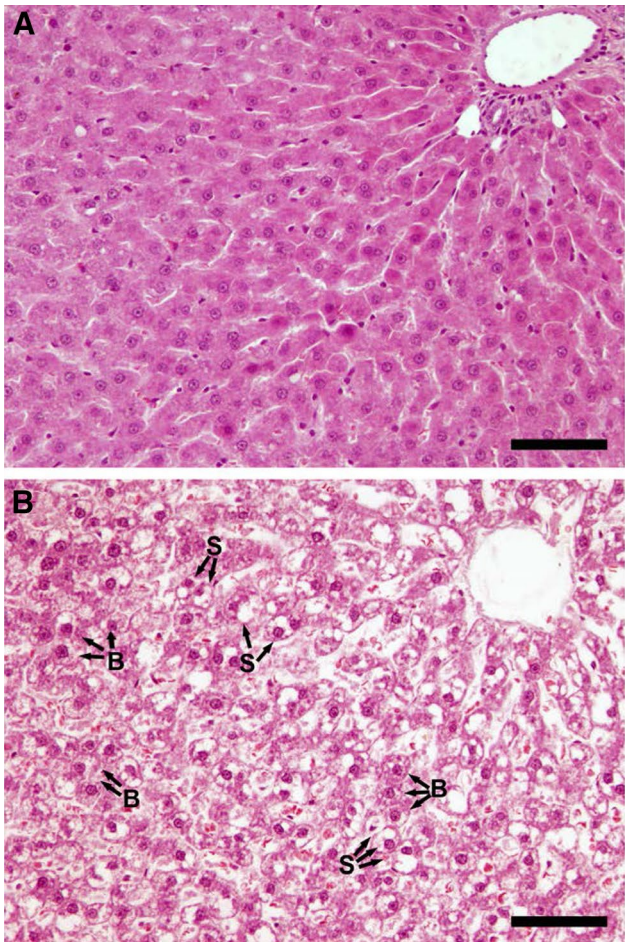

Fig. 4 Histological analysis of the liver. Hematoxylin–eosin staining of CT **a** and CAF-fed rats **b**. Hepatocyte steatosis (score = 3) and cellular ballooning (score = 2) are evident in the liver of CAF group. Arrows indicate steatosis (S) and ballooning (B). *CAF* cafeteria diet + cola-based soft drink (n = 20); *CT* control diet (n = 16); calibration bars = 100 µm

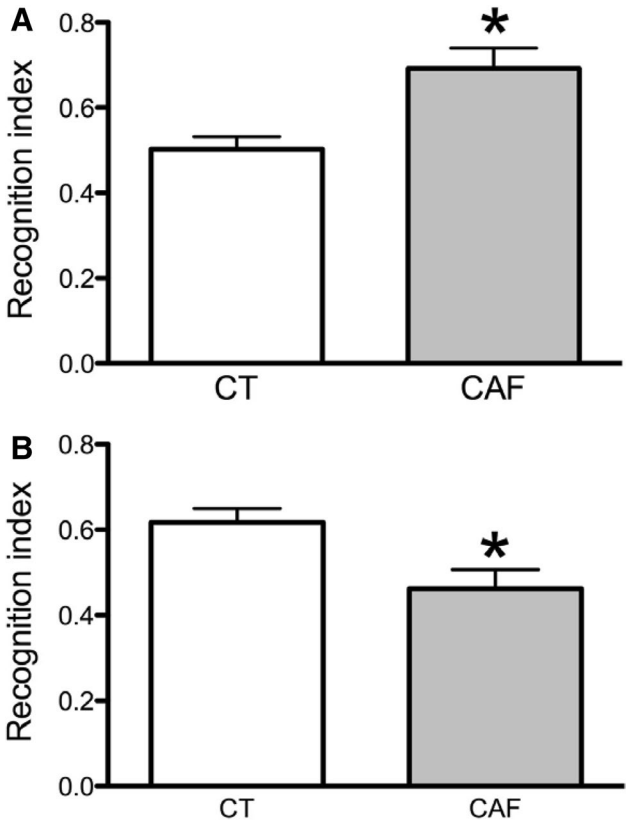

Fig. 5 Effects of different soft-drinks on long-term recognition memory. **a** CAF-fed rats that consumed a cola-based soft drink showed significantly higher recognition index when compared to CT group. **b** CAF-fed rats that consumed an orange-based soft drink showed significantly lower recognition index when compared to CT group. Data are expressed as mean ± SEM. n = 10 per group. *CAF* cafeteria diet, *CT* control diet; *p < 0.05

of brain-derived neurotrophic factor, altered glutamatergic signaling, impaired insulin regulation and TNF-α overexpression [5]. Insulin administration can improve memory, as demonstrated by an enhancement in the passive avoidance task in rats. However, the induction of hippocampal-specific insulin resistance can compromise the synaptic plasticity, which impairs spatial learning and memory [19]. Another important factor that can influence the object recognition (OR) test is the action of leptin, which was elevated in the CAF group in the present study. It has been demonstrated that increased levels of leptin in the brain can impact learning and memory, and the hippocampus has the highest synthesis of its receptors in the CNS. Studies propose that leptin modulates plasticity in learning and memory based behavioral tasks, so that obese rodents with deficiency of its receptors show impairments in hippocampal long-term potentiation (LTP), which is responsible for memory formation [20]. Our results in the OR test show that CAF-fed rats, that received different soft drinks, presented distinct outcomes. Surprisingly, the rats who had free access to cola-based beverage had a better performance on the object recognition test, indicating that cola beverage improved CAF-fed rats recognition memory.

One important component of cola based soft drinks is caffeine, which is one of the most widely consumed supplements in the world [21]. Caffeine is able to cross the BBB [22] and exerts its effects acting as an antagonist of A1 and A2 adenosine receptors. A1 receptors are located in all parts of the brain with higher concentrations in the hippocampus, cerebral and cerebellar cortices, and certain thalamic nuclei, whereas A2 subtypes are located in the dopamine-rich regions of the brain [23]. As an adenosine receptor antagonist caffeine can promote excitation of striatonigral neuronal projections and reduce inhibitory signals to striatopallidal neurons [11].

Recent studies indicate the risks related to the ingestion of soft drinks. For instance, soft drinks containing sodium

benzoate (SB), a commonly used food preservative, can impair memory and motor coordination [24]. Pase et al. also linked the cumulative intake of artificially sweetened soft drinks with a higher risk of stroke and dementia in humans [25]. Furthermore, the consumption of soft drinks containing sugar and caffeine is capable of causing worse sleep pattern and quality, especially in students [26]. On the other hand, in healthy human subjects, caffeine has shown to possess positive effects on long-term retention by enhancing memory consolidation [27]. In obese individuals, the apparent volume of distribution of caffeine is increased by 60%, but obesity has no effect on caffeine clearance and seems to prolong its half-life by 31–69% [28]. Hameleers et al. also observed that habitual caffeine consumption was associated with better long-term verbal memory [29]. In addition, it was shown that sucrose ingestion caused memory impairment, while rats receiving sucrose combined with caffeine exhibited a cognitive performance similar to control group [30]. These findings indicate that caffeine may protect against sucrose-evoked cognitive impairments, which corroborate with our results. Also, Alzoubi et al. found that caffeine prevents short and long-term memory impairments induced by chronic l-methionine administration. Authors infer that caffeine would be able to preventing reduction in antioxidant protection mechanisms in the hippocampus, during chronic l-methionine administration [31]. Here, CAF-fed rats had higher levels of lipid peroxidation in the liver and it was not affected by the cola-based soft drink consumption.

It is well established plasma levels of leptin are proportional to body fat content. Accordingly, we showed the amount of visceral adipose tissue as well as the plasma levels of leptin are higher in CAF-fed animals. Leptin has an inhibitory effect on insulin synthesis. Insulin pancreatic secretion leads to lipid storage and leptin production in the adipocytes, generating a regulatory process between β-cells and adipocytes. The administration of leptin reduces circulating insulin levels in inheritable obese phenotype mouse, and simultaneously leads to acute increase in blood glucose levels [32]. In our study we verified CAF induced hyperglycemia and decreased insulin plasma levels. Thus, the lower insulin levels may be caused by increased leptin, but it also might be a result of pancreatic dysfunction, since CAF model is highly obesogenic [33]. Inflammatory processes are usually supposed to be a consequence of obesity. In fact, chronic inflammation in adiposity can lead to insulin resistance and other obesity-related issues, denominated metabolic syndrome. Although, the source of this inflammatory event is not known, studies have evidenced that oxidative stress could be involved in pro-inflammatory status [34].

Oxidative stress is the most important event leading to complications in diet-induced obesity in rats. It has been demonstrated that oxidative stress caused by a high fat diet increases glucose intolerance and insulin resistance, and also rises plasma and tissues levels of oxidative stress markers [1]. Hypercaloric diets can lead to oxidative stress by increasing lipid peroxidation. Moreover, the fat consumption may modify cellular levels of pro and antioxidant substances, making cell membranes more susceptible to oxidation reactions [35]. It was previously demonstrated that CAF increased lipid peroxidation in the liver, testicles and kidney [16]. Ulla et al. also showed that obesity rises lipid peroxidation in hepatic tissues, as expressed by increased levels of MDA [1]. These studies are in accordance to our results, in which CAF-fed rats had higher levels of lipid peroxidation in the liver.

As mentioned before, obesity is an important risk factor for increasing lipid peroxidation and decreasing the activity of cytoprotective enzymes. Thus, CAF can induce inflammation, steatosis and fibrosis in the liver. Ulla et al. demonstrated, by histological analysis, that high carbohydrate and fat diet induced obesity in rats, and the animals presented inflammatory cells infiltration in the liver and lipid accumulation in hepatocytes [1]. Parafati et al. demonstrated the presence of liver fibrosis in CAF treated rats [36]. It corroborates with our histological evaluation of the liver, showing the presence of low lobular inflammatory infiltrate, hepatocellular ballooning and intense steatosis in CAF-fed rats, characterizing a nonalcoholic steatohepatitis (NASH). Thus, our results showed that 16 weeks of CAF is able to induce NASH which corroborates with previous studies, indicating that CAF is an important model to study fatty liver diseases.

Milagro et al. showed a correlation between hepatic lipid peroxidation and serum leptin levels, suggesting a possible link between adipose tissue and liver [34]. Leptin leads to insulin resistance and hepatic disease in both, cell cultures and animal models, by activating the transforming growth factor β axis and stellate cells. Serum leptin is related to liver steatosis, but not fibrosis, in NASH [37]. Our results show an increase in serum leptin levels in the CAF group, confirming its possible correlation to our histological findings.

In summary, CAF induced an increase in weight gain and visceral adiposity, as well as, hyperglycemia, hypertriglyceridemia, and increased leptin levels, proving that this model is consistent to induce obesity in rats. We also found increased lipid peroxidation in the liver and pathological characteristics of NAFLD. Based on our findings, cola-based soft drink could provide an improvement in recognition memory of obese animals. Conversely, an orange-based soft drink used as part of CAF showed opposite results. It suggests caffeine may protect the CNS from the declarative memory decline caused by obesity. However, more studies are necessary to assess the benefits of caffeine supplementation in obese subjects. Thus, besides being a widely used model for the study of brain function in obesity, the composition of the CAF should be taken into account when analyzing the neurological impact of this hypercaloric diet.

Acknowledgments This study was supported by the Brazilian National Council for Scientific and Technological Development (CNPq), the Coordination for the Improvement of Higher Education Personnel (CAPES) and the Foundation for Research Support of the State of Rio Grande do Sul (FAPERGS).

Author Contributions GSF, ACM performed experiments, analyzed data, and wrote the manuscript. SO, RT, EES and FF performed experiments. MG and MP contributed to data analysis and editing of the manuscript. RPG designed the study, interpreted the results and wrote the manuscript. All authors read and approved the final manuscript.

Funding This study was supported by the Brazilian National Council for Scientific and Technological Development (CNPq), the Coordination for the Improvement of Higher Education Personnel (CAPES) and the Foundation for Research Support of the State of Rio Grande do Sul (FAPERGS).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest regarding this study.

Ethical Approval All efforts were made to minimize animal suffering and to reduce the number of animals used in the experiments, which were performed in accordance with the international laws for the care of laboratory animals, following the 3Rs guidelines. All procedures were approved by the Institutional Animal Care and Use Committee (UFCSPA, Brazil, protocol No.536/17). This article does not contain any studies with human participants performed by any of the authors.

References

1. Ulla A, Alam MA, Sikder B, Sumi FA, Rahman MM, Habib ZF, Mohammed MK, Subhan N, Hossain H, Reza HM (2017) Supplementation of Syzygium cumini seed powder prevented obesity, glucose intolerance, hyperlipidemia and oxidative stress in high carbohydrate high fat diet induced obese rats. BMC Complement Altern Med 17:289. https://doi.org/10.1186/s12906-017-1799-8
2. Guillemot-Legris O, Muccioli GG (2017) Obesity-induced neuroinflammation: beyond the hypothalamus. Trends Neurosci 40:237–253. https://doi.org/10.1016/j.tins.2017.02.005
3. Beydoun MA, Beydoun HA, Wang Y (2008) Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obes Rev 9:204–218. https://doi.org/10.1111/j.1467-789X.2008.00473.x
4. Kanoski SE, Zhang Y, Zheng W, Davidson TL (2010) The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. J Alzheimers Dis 21:207–219. https://doi.org/10.3233/jad-2010-091414
5. Kanoski SE, Davidson TL (2011) Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. Physiol Behav 103:59–68. https://doi.org/10.1016/j.physbeh.2010.12.003
6. Anjum I, Fayyaz M, Wajid A, Sohail W, Ali A (2018) Does obesity increase the risk of dementia: a literature review. Cureus 10:e2660. https://doi.org/10.7759/cureus.2660
7. Lutz TA, Woods SC (2012) Overview of animal models of obesity. Curr Protoc Pharmacol 58(1):5–61. https://doi.org/10.1002/0471141755.ph0561s58
8. Bortolin RC, Vargas AR, Gasparotto J, Chaves PR, Schnorr CE, Martinello KB, Silveira AK, Rabelo TK, Gelain DP, Moreira JCF (2018) A new animal diet based on human Western diet is a robust diet-induced obesity model: comparison to high-fat and cafeteria diets in term of metabolic and gut microbiota disruption. Int J Obes (Lond) 42:525–534. https://doi.org/10.1038/ijo.2017.225
9. Moore BJ (1987) The cafeteria diet—an inappropriate tool for studies of thermogenesis. J Nutr 117:227–231. https://doi.org/10.1093/jn/117.2.227
10. Popkin BM (2010) Patterns of beverage use across the lifecycle. Physiol Behav 100:4–9. https://doi.org/10.1016/j.physbeh.2009.12.022
11. McLellan TM, Caldwell JA, Lieberman HR (2016) A review of caffeine's effects on cognitive, physical and occupational performance. Neurosci Biobehav Rev 71:294–312. https://doi.org/10.1016/j.neubiorev.2016.09.001
12. Ennaceur A, Delacour J (1988) A new one-trial test for neurobiological studies of memory in rats 1. Behavioral data. Behav Brain Res 31:47–59
13. Buege JA, Aust SD (1978) Microsomal lipid peroxidation. Methods Enzymol 52:302–310
14. Bradford MM (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 72:248–254
15. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ (2005) Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 41:1313–1321. https://doi.org/10.1002/hep.20701
16. Andrade GF, de Almeida C, Espeschit AC, Dantas MI, Benjamin Ldos A, Ribeiro SM, Martino HS (2013) The addition of whole soy flour to cafeteria diet reduces metabolic risk markers in wistar rats. Lipids Health Dis 12:145. https://doi.org/10.1186/1476-511x-12-145
17. Virtuoso A, Forkman B, Sarruf DA, Tveden-Nyborg P, Sørensen DB (2018) A cafeteria diet alters the decision making strategy and metabolic markers in Sprague-Dawley male rats. Appl Anim Behav Sci 199:35–44. https://doi.org/10.1016/j.applanim.2017.10.012
18. Hargrave SL, Davidson TL, Lee TJ, Kinzig KP (2015) Brain and behavioral perturbations in rats following Western diet access. Appetite 93:35–43. https://doi.org/10.1016/j.appet.2015.03.037
19. Mandal A, Prabhavalkar KS, Bhatt LK (2018) Gastrointestinal hormones in regulation of memory. Peptides 102:16–25. https://doi.org/10.1016/j.peptides.2018.02.003
20. Van Doorn C, Macht VA, Grillo CA, Reagan LP (2017) Leptin resistance and hippocampal behavioral deficits. Physiol Behav 176:207–213. https://doi.org/10.1016/j.physbeh.2017.03.002
21. Fulgoni VL III, Keast DR, Lieberman HR (2015) Trends in intake and sources of caffeine in the diets of US adults: 2001–2010. Am J Clin Nutr 101:1081–1087. https://doi.org/10.3945/ajcn.113.080077
22. Fredholm BB (1995) Astra Award Lecture. Adenosine, adenosine receptors and the actions of caffeine. Pharmacol Toxicol 76:93–101
23. Ludwig IA, Clifford MN, Lean ME, Ashihara H, Crozier A (2014) Coffee: biochemistry and potential impact on health. Food Funct 5:1695–1717. https://doi.org/10.1039/c4fo00042k
24. Khoshnoud MJ, Siavashpour A, Bakhshizadeh M, Rashedinia M (2018) Effects of sodium benzoate, a commonly used food preservative, on learning, memory, and oxidative stress in brain of mice. J Biochem Mol Toxicol 32:e22022. https://doi.org/10.1002/jbt.22022
25. Pase MP, Himali JJ, Beiser AS, Aparicio HJ, Satizabal CL, Vasan RS, Seshadri S, Jacques PF (2017) Sugar- and artificially sweetened beverages and the risks of incident stroke and dementia:

a prospective cohort study. Stroke 48:1139–1146. https://doi.org/10.1161/strokeaha.116.016027
26. Faris MAE, Jahrami H, Al-Hilali MM, Chehyber NJ, Ali SO, Shahda SD, Obaid RS (2017) Energy drink consumption is associated with reduced sleep quality among college students: a cross-sectional study. Nutr Diet 74:268–274. https://doi.org/10.1111/1747-0080.12289
27. Borota D, Murray E, Keceli G, Chang A, Watabe JM, Ly M, Toscano JP, Yassa MA (2014) Post-study caffeine administration enhances memory consolidation in humans. Nat Neurosci 17:201–203. https://doi.org/10.1038/nn.3623
28. Kamimori GH, Somani SM, Knowlton RG, Perkins RM (1987) The effects of obesity and exercise on the pharmacokinetics of caffeine in lean and obese volunteers. Eur J Clin Pharmacol 31:595–600
29. Hameleers PA, Van Boxtel MP, Hogervorst E, Riedel WJ, Houx PJ, Buntinx F, Jolles J (2000) Habitual caffeine consumption and its relation to memory, attention, planning capacity and psychomotor performance across multiple age groups. Hum Psychopharmacol 15:573–581. https://doi.org/10.1002/hup.218
30. Xu TJ, Reichelt AC (2018) Sucrose or sucrose and caffeine differentially impact memory and anxiety-like behaviours, and alter hippocampal parvalbumin and doublecortin. Neuropharmacology 137:24–32. https://doi.org/10.1016/j.neuropharm.2018.04.012
31. Alzoubi KH, Mhaidat NM, Obaid EA, Khabour OF (2018) Caffeine prevents memory impairment induced by hyperhomocysteinemia. J Mol Neurosci 66:222–228. https://doi.org/10.1007/s12031-018-1158-3
32. Denroche HC, Huynh FK, Kieffer TJ (2012) The role of leptin in glucose homeostasis. J Diabetes Investig 3:115–129. https://doi.org/10.1111/j.2040-1124.2012.00203.x
33. Alempijevic T, Dragasevic S, Zec S, Popovic D, Milosavljevic T (2017) Non-alcoholic fatty pancreas disease. Postgrad Med J 93:226–230. https://doi.org/10.1136/postgradmedj-2016-134546
34. Milagro FI, Campion J, Martinez JA (2006) Weight gain induced by high-fat feeding involves increased liver oxidative stress. Obesity (Silver Spring) 14:1118–1123. https://doi.org/10.1038/oby.2006.128
35. Moreira EA, Fagundes RL, Filho DW, Neves D, Sell F, Bellisle F, Kupek E (2005) Effects of diet energy level and tomato powder consumption on antioxidant status in rats. Clin Nutr 24:1038–1046. https://doi.org/10.1016/j.clnu.2005.08.005
36. Parafati M, Lascala A, La Russa D, Mignogna C, Trimboli F, Morittu VM, Riillo C, Macirella R, Mollace V, Brunelli E, Janda E (2018) Bergamot polyphenols boost therapeutic effects of the diet on non-alcoholic steatohepatitis (NASH) induced by "Junk Food": evidence for anti-inflammatory activity. Nutrients 10(11):1604. https://doi.org/10.3390/nu10111604
37. Chitturi S, Farrell G, Frost L, Kriketos A, Lin R, Fung C, Liddle C, Samarasinghe D, George J (2002) Serum leptin in NASH correlates with hepatic steatosis but not fibrosis: a manifestation of lipotoxicity? Hepatology 36:403–409. https://doi.org/10.1053/jhep.2002.34738

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.