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Cafeteria diet administered from lactation to adulthood promotes a change in risperidone sensitivity on anxiety, locomotion, memory, and social interaction of Wistar rats

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ABSTRACT

Purpose: To evaluate the nutritional status and behavior of animals fed a cafeteria diet from the onset of lactation after the addition of risperidone.
Methods: During the lactation period, 14 litters of Wistar rats (dam + 8 pups) were fed one of two diets: control (CTRL; $n = 7$) or cafeteria (CAF; $n = 7$). After weaning, the males were placed in individual cages, receiving the same diet as offered to their respective dams. Food and caloric intake, body weight, feed and energy efficiency, and adipose tissue weight were evaluated in the male offspring. In adulthood, they were assigned to receive treatment with saline (CTRL-S, CAF-S) or risperidone (CTRL-R, CAF-R) ($n = 21$ in each group). They then underwent behavioral testing, which included the elevated plus maze, open field, object recognition, and social interaction tests. Variance analysis (ANOVA) was used, followed by Newman–Keuls when p-values were < 0.05.
Results: The CAF group exhibited higher caloric intake, weight gain, feed efficiency, and adipose tissue than the CTRL group. The animals in the CAF group exhibited oxidative stress characteristics in the hippocampus, which may have compromised the function of this structure and promoted behavioral changes. The CAF-S group exhibited anxiety, as indicated by the greater number of entrances and time spent in the center of the open field. They also showed greater locomotion through a greater number of quadrants traveled. CAF-S animals also demonstrated memory impairments, assessed using the object recognition test, and decreased social interaction. The CAF-R group demonstrated anxiety and decreased locomotion in the open field. There was a decrease in their interaction with both objects in the object recognition test. The CAF-R group obtained greater sociability in the social interaction test. Such effects may be associated with changes in the serotonergic system of these animals.
Conclusion: Risperidone administered to animals on a cafeteria diet led to a greater reduction in locomotion, had an anxiogenic effect, caused impaired memory, and improved social interaction.

1. Introduction

The periods of lactation and early childhood are considered crucial in brain formation, because they form the basis of cognitive, motor, social, and emotional development. Adequate nutrition during these phases is paramount for brain maturation [1]. For this to occur, the

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mother must have a balanced diet and consume all the nutrients in the correct amounts [2, 3], avoiding excess consumption of simple sugars and saturated fats [4]. An unbalanced maternal diet can culminate in significant changes at the cellular, structural, metabolic, and behavioral levels in the offspring, especially when the animal is exposed to the diet for a longer time, starting early in life and continuing into adulthood [5, 6].

According to Rivera [7], maternal diets rich in fat can be understood as unbalanced or obesogenic and may influence the behavior and mental health of a developing offspring. Several studies have already demonstrated changes in anxiety, locomotion, memory, and social interaction in the offspring of rodents exposed to obesogenic diets during gestation, lactation, and/or the post-lactation period [6, 8–10].

One mechanism that may be involved in certain behavioral changes is related to redox status and the impairment of neurotransmitter circuits in the brain [7]. An obesogenic diet can increase levels of reactive oxygen species (ROS), which can in turn compromise the development and function of the neurotransmitter circuits responsible for behavior and emotions, such as the serotonergic system [11–13].

Serotoninergic drugs are commonly used to treat these behavioral/neuropsychiatric disorders [14]. In this regard, risperidone is a second-generation antipsychotic drug that shows high-affinity antagonistic action on serotonergic receptors ($5HT_{2A}$) [15, 16]. It is a well-established treatment option in a broad spectrum of psychiatric/behavioral diseases [16], such as psychosis [16], autism [17], attention deficit hyperactivity disorder [18, 19], and acute agitation [15]. However, no studies have investigated the effect of these drugs in the offspring of mothers on an obesogenic diet from the beginning of life until adulthood.

The present study aimed to evaluate the effect of risperidone – a serotonergic drug – on the behavior of rats fed an obesogenic diet (cafeteria diet) from lactation to adulthood (pre- and post-weaning).

2. Materials and methods

2.1. Ethics

This project was developed in the Experimental Nutrition Laboratory (LabNutrex) of Federal University of the Valleys of Jequitinhonha and Mucuri (UFVJM). Management and euthanasia were carried out according to the ethical principles of animal use [20], and the study was approved by the Ethics Committee on the Use of Animals of UFVJM (protocol 041/16). All animals used were obtained from LabNutrex/UFVJM and housed in conditions of natural moisture at a temperature of 22 ± 2 °C (controlled by an air conditioner). They were subjected to a 12-hour cycle of light and darkness, with the light cycle beginning at 6:00 a.m.

2.2. Animals and diets

Female Wistar rats (Rattus norvegic*us*) were placed for mating with males at the age of 80 days (two females per male). During mating and gestation, these animals received a standard diet (Nuvilab® CR-1). After delivery, which was considered "day 0″ (D0) of the experiment, the litters were culled to eight pups (six males, two females). Fourteen litters were included in the study. During the lactation period (D0–D21), dams and their litters were divided into (1) a control group (CTRL; $n = 7$), which received lab chow (Nuvilab® CR-1; 3.43 kcal/g – protein 0,83 kcal/g; carbohydrates 1,95 kcal/g; fats 0,65 kcal/g) and water *ad libitum*, and (2) a cafeteria group (CAF), which received a cafeteria diet (4.74 kcal/g – protein 0,65 kcal/g; carbohydrates 1,88 kcal/g; fats 2,21 kcal/g) and water *ad libitum* ($n = 7$). The cafeteria diet consisted of lab chow (Nuvilab®), milk chocolate (Bel®), peanuts (Pachá®), and sweet biscuit (Aymoré®), all bought at the local store. The cafeteria diet was prepared weekly, with all the components mixed, pelleted, and supplied to the animals [21, 22].

On the 21st day of life, the rats were weaned, and the male pups ($n = 84$) were placed in individual boxes, receiving the same diet as their mother until adulthood (CTRL offspring $n = 42$; CAF offspring $n = 42$). The female pups were used in another study.

2.3. Nutritional evaluations

After weaning, the male offspring were weighed individually once a week, and their body weight gain was determined by the difference in weight between D21 and D114. The food (lab chow and cafeteria diet) was weighed daily to ensure correct food amount and calorie intake. All of these evaluations (food and body weight) were performed in the morning (08:00 a.m. to 12:00 a.m.). Feed and energy efficiency measurements evaluate the efficiency of a particular diet in promoting weight gain. In the present study, it was calculated as the ratio of weight gain to total food intake or total caloric intake.

2.4. Behavioral evaluations

The animals performed the behavioral tests between D114 and D118. Each animal received one of the following treatments intraperitoneally 30 min before each test: 1.0 $mL.kg^{-1}$ of saline or risperidone (Sandoz®; 0.1 $mg.kg^{-1}$) [23–25], in addition, it is emphasized that an equivalent number of animals from a particular mother received each treatment (saline or risperidone). Thus, the following groups were formed: control saline (CTRL-S), fed a control diet and administered saline ($n = 21$); control risperidone (CTRL-R), fed a control diet and administered risperidone ($n = 21$); cafeteria saline (CAF-S), fed a cafeteria diet and administered saline ($n = 21$); cafeteria risperidone (CAF-R), fed a cafeteria diet and administered risperidone ($n = 21$). Half of the animals in each group first performed the elevated plus maze (EPM) test on D114, followed by the social interaction tests on D118 (the same animals that were tested in EPM and social interaction test), whereas the other half performed the open field (OF) test on D115 and the novel object recognition (NOR) test on D115–D117. Approximately half of the animals in the same litter received saline treatment, while the other half received risperidone.

After receiving the treatment, each animal was placed in the behavior room 15 min prior to the tests' start, allowing them to acclimatize. All tests were performed in a double-blind manner, in an isolated room, in the presence of light (150 lx), and between 08:00 a.m. and 12:00 a.m.

2.4.1. EPM test

Each animal was placed in the maze with its head facing towards one of the closed arms; its movements were filmed for 300 s. At the end of each test, the maze was cleaned using 70% alcohol to eliminate olfactory signals. Trained observers evaluated the number of entries, with one entry defined as the animal entering with all four paws, and the time spent in each arm. We then calculated the ratio of entries into the open arms to entries into the closed arms, as well as the ratio of time spent inside the open arms to time spent in the closed arms.

2.4.2. Social interaction test

We selected pairs of animals of the same sex and similar weights who had not yet come into contact. Each animal was marked with a different color pen at the proximal height of the tail (red or black) 1 h before the start of the experiment (26). The test was performed in a polypropylene box that contained clean shavings, and the animals' movements were filmed for 600 s. We recorded the number of times and the total time that one animal exhibited the following active social interaction behaviors: sniffing/licking/touching the anogenital region of the other, sniffing/licking/touching the other animal's snout, sniffing/licking/touching the other animal's body with the muzzle, mounting/rolling over the other animal. Finally, we evaluated the number of times and the total time of the animal's active social interaction.

2.4.3. OF test

Each animal was placed in the OF and its movements were filmed for 600 s. At the end of the test, the arena was cleaned using 70% alcohol. We observed the number of entries and the time spent in the center of the OF (considered as the animal inserting all four paws in the central zone), as well as the total number of quadrants crossed (distance covered).

2.4.4. NOR tests

Twenty-four hours after exposure in the OF (step 1: habituation), the same animals were re-exposed to the arena for 600 s (step 2: familiarization), with a ball (rubber, green color, spherical shape) and a piece of Lego® (plastic, red rectangle) on the floor. These objects were referred to as "A" and "B", respectively. The animals were returned to their home cages after the exposure time. Twenty-four hours later, the animals were placed back into the arena for 300 s (step 3: recognition test), this time with only one familiar object (object A) and a new object: a pyramid (white crystal), referred to as object "C". The animal's active interaction with each of the objects – that is, the time spent exploring them – was evaluated, with the following being considered as exploration actions: smelling, licking, biting, and touching the object with the snout or paw.

2.5. Euthanasia and collection of biological samples

The animals were euthanized by decapitation on D120. Their brains were rapidly withdrawn (< 3 min) and dipped in phosphate buffered saline (PBS; 50 mM, pH 7.0) at 4 °C. Thereafter, the structures of the prefrontal cortex and hippocampus were dissected and stored at −80 °C for subsequent analyses [27]. The animals' abdominal adipose tissue (visceral, retroperitoneal and epididymal) was also removed and weighed.

2.5.1. Redox status of the brain (prefrontal cortex and hippocampus)

After the prefrontal cortex and hippocampus were removed, oxidative stress markers were evaluated in these tissues. Malondialdehyde (MDA) levels were estimated according to Buege and Aust [28]. Carbonylated protein levels were examined following the methodology published by Sohal et al. [29] and Levine et al. [30]. The total protein level was determined according to the method proposed by Bradford [31]. We evaluated the activity of the antioxidant enzymes superoxide dismutase (SOD) and glutathione S-transferase (GST). SOD levels were estimated based on both H_2O_2 production and SOD reduction to nitroblue tetrazolium [32]. GST activity was assessed as described by Habig et al. [33] and calculated in terms of the average oxidation of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH).

2.5.2. Serotonin

Brain tissues (prefrontal cortex and hippocampus) were weighed and homogenized in a phosphate-buffered saline (PBS) solution (50 mM, pH 7.0). We detected serotonin (serotonin hydrochloride powder H9523; Sigma-Aldrich®) in the samples using the differential pulse voltammetry (DPV) technique. The voltammetric measurements were carried out on an Autolab® PGSTAT 128 N potentiostat/galvanostat (Utrecht, Netherlands), which was operated using Autolab Nova version 1.10 software for data collection and analysis. The electrochemical experiments were performed in a one-compartment glass cell (20.0 mL) mounted with three electrodes: an Ag/AgCl (3.0 mol.L^{-1} KCl) reference electrode, a counter electrode composed of a 1.0 cm^2 Pt foil, and a boron-doped diamond electrode as a working electrode. All voltammetric measurements were conducted at room temperature.

2.6. Statistical analysis

We used GraphPad Prism® 7.0 to analyze the data and prepare the figures. We used analysis of variance to evaluate the differences between the groups, followed by the Newman–Keuls test when the *p*-value was < 0.05. All results are shown as mean ± standard error of the mean.

Table 1
Male offspring nutritional evaluations from weaning until adulthood (D21-D114) and adipose tissue weight (D120).

Variables	CTRL	CAF
Total food intake (g)	2184.24 ± 44.51[a]	1693.15 ± 30.94[b]
Total calorie intake (kcal)	7491.94 ± 152.67[b]	8025.55 ± 146.66[a]
Initial weight* (g)	46.41 ± 1.04[a]	41.36 ± 0.79[a]
Weight gain (g)	332.56 ± 9.43[b]	359.27 ± 7.34[a]
Feed efficiency (g/g)	0.15 ± 0.01[b]	0.21 ± 0.01[a]
Energy efficiency (g/kcal)	0.04 ± 0.01[a]	0.04 ± 0.01[a]
Adipose tissue** (g)	23.61 ± 1.50[b]	39.37 ± 3.72[a]

Control (CTRL) and Cafeteria (CAF), n = 20–21. Different letters on the same line indicate significant difference by the Newman Keuls test ($p < 0.05$).

* Initial weight was defined as weight on the 21st day (D21) of life of the animals;.

** Retroperitoneal, visceral and epididymal adipose tissue.

3. Results

The CAF group showed lower total food intake ($p < 0.001$) and higher calorie intake ($p < 0.05$) than the CTRL group. Weight gain ($p < 0.05$), feed efficiency ($p < 0.001$), and abdominal adipose tissue ($p < 0.001$) were higher in the CAF group than in the CTRL group (Table 1).

There was no significant difference among the groups regarding the ratio of entries into each arm of the EPM (Fig. 1A and 1B). The ratio of time spent in each arm differed significantly among the groups ($p < 0.05$), with CTRL-R group showing the highest percentage of time spent in the open arm (Fig. 1D).

The number of entries into the central area of the OF ($p < 0.01$) differed significantly among the groups, with the CAF-S group showing the most entries, as shown in Fig. 2A. A significant difference was also found in the ratio of time spent ($p < 0.01$) in the central zone. The CAF-S group had the highest value in this instance, followed by the CTRL-S and CTRL-R groups, and finally by the CAF-R group (Fig. 2B).

The total number of quadrants covered in the OF test showed a significant difference among the groups ($p < 0.01$). The highest distance was covered by the CAF-S group, followed by the CTRL-S, CTRL-R, and CAF-R groups (Fig. 2C).

No significant differences were detected in the exploration time of objects A and B in the familiarization phase of the object recognition test (Fig. 3A). In the test phase, the CTRL-S group presented a longer exploration time ($p < 0.001$) for object C (novel object) than for object A (familiar object), while the CTRL-R, CAF-S, and CAF groups displayed no difference in exploration time between the two objects (Fig. 3B).

The behaviors evaluated in the social interaction test are shown in Table 2. There was no significant difference among the groups regarding the frequency of any of these interactions (anogenital, body, snout, mounting/rolling). However, anogenital interaction was lower in the CAF-S and CAF-R groups than the other groups, in relation to the time in which these interactions occurred ($p < 0.05$).

The number of total social interactions differed significantly between the groups ($p < 0.05$), with CAF-S showing the lowest number. The total interaction time was higher for CTRL-S than for CAF-S and CAF-R, with a significant difference ($p < 0.05$) (Fig. 4).

In the evaluation of brain redox status (prefrontal cortex and hippocampus), GST enzyme levels in the pre-frontal cortex were greater in the CAF group than in the CTRL group ($p < 0.05$). In the hippocampus, the levels of MDA ($p < 0.05$) and SOD ($p < 0.05$) were higher in the CAF group than in the CTRL group (Table 3).

Analyzing brain samples from male offspring using DPV showed no difference in serotonin levels between the groups, for both prefrontal cortex and hippocampus (Fig. 5).

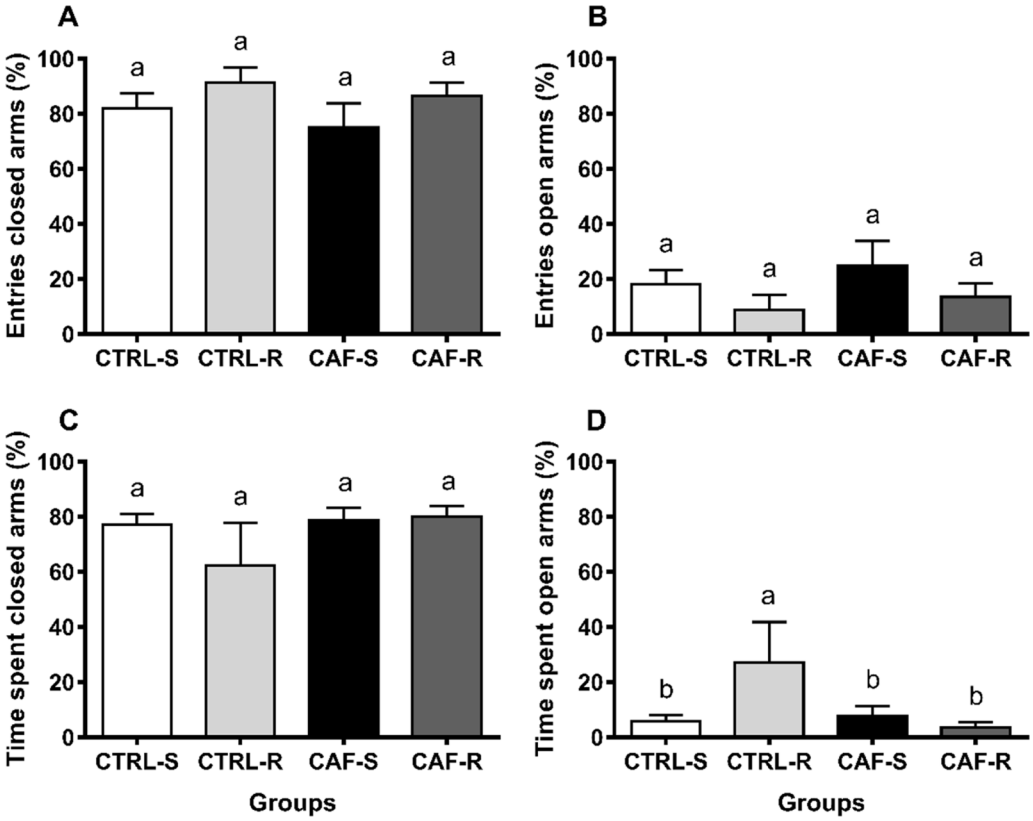

Fig. 1. Ratio of entries in closed (A) and open (B) arms; ratio of time spent in closed (C) and open (D) arms in the EPM test on D114 (n = 10–11). Legend: Control saline (CTRL-S); Control risperidone (CTRL-R); Cafeteria saline (CAF-S); Cafeteria risperidone (CAF-R). Different letters between the columns indicate a statistically significant difference by the Newman Keuls test ($p < 0.05$).

4. Discussion

Cafeteria diets are mainly used in the literature to study obesity. However, in recent years, this Western diet model has also been linked to behavioral changes in animals. In this context, the present study presented a model of the cafeteria diet with longer duration of exposure, comprising the lactation, post-lactation, and adult life stages of the animals. Alongside obesity, this treatment led to differences in the

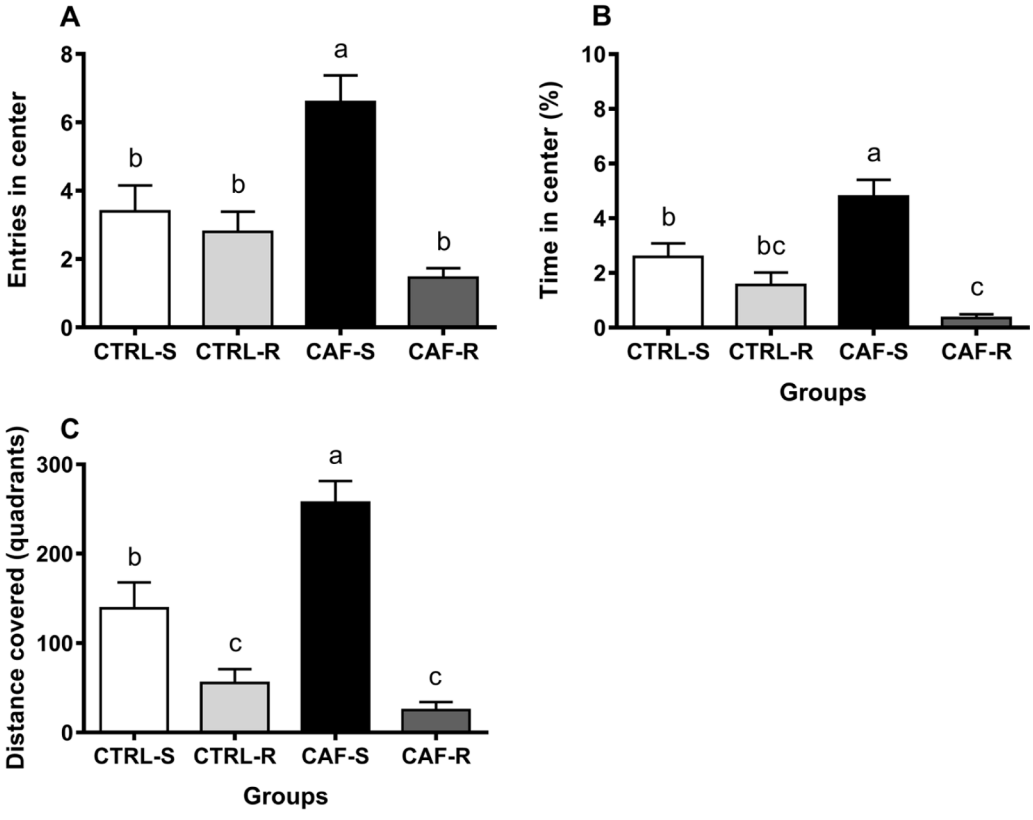

Fig. 2. Entries (A) and ratio of time spent (C) in the center; and quadrants covered in the OF test on D115 (n = 10–11). Legend: Control saline (CTRL-S); Control risperidone (CTRL-R); Cafeteria saline (CAF-S); Cafeteria risperidone (CAF-R). Different letters between the columns indicate a statistically significant difference by the Newman Keuls test ($p < 0.05$).

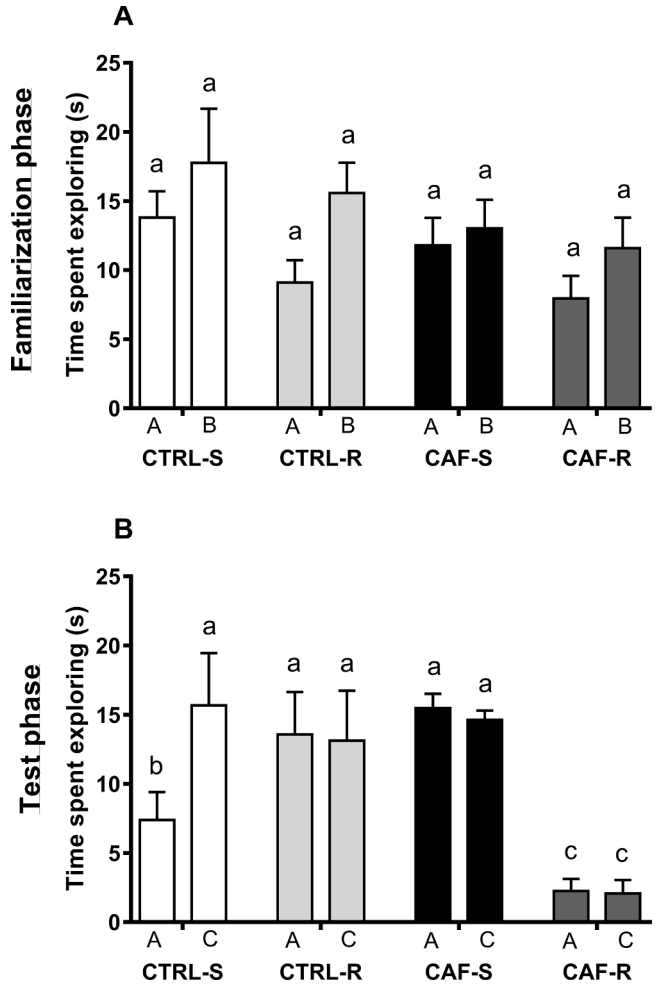

Fig. 3. Exploration time for objects A and B during the familiarization phase (A), and exploration time for objects A (familiar object) and C (novel object) during the test phase (B) in the NOR test on D117 (n = 10–11). Legend: Control saline (CTRL-S); Control risperidone (CTRL-R); Cafeteria saline (CAF-S); Cafeteria risperidone (CAF-R). Different letters between the columns indicate a statistically significant difference by the Newman Keuls test ($p < 0.05$).

sensitivity of risperidone compared to animals fed a standard diet.

Lower feed intake in animals that receive a cafeteria diet has already been reported in the literature. Souza et al. [34] used a cafeteria diet similar to that in the present study, finding lower food intake in the CAF group after eight weeks. Even though the food had high palatability, consisting of chocolate, peanuts, and biscuits, the cafeteria diet did not promote higher net food intake (in grams), perhaps because it has higher calorie density (4.74 kcal/g) than lab chow (3.44 kcal/g). However, slightly more energy was consumed by rats raised on cafeteria diet.

The CAF group demonstrated a higher calorie intake, corroborating previous studies [6, 35]. Rats tend only to ingest food according to their energy needs [36], so an above-standard calorie intake can be characterized as a hyperphagic state. Cafeteria diets are rich in foods that contain large amounts of simple sugars and saturated fats, which favor weight gain, as demonstrated in the CAF group of the present study. Mucellini et al. [37] administered a more varied cafeteria diet and observed weight gain after 120 days of treatment, consistent with the present study results. Additionally, the CAF diet demonstrated greater food efficiency, since the animals who received this diet required less food to gain more weight.

The accumulation of adipose tissue, especially in the abdominal region, is one of the main factors that defines an individual as obese. In particular, a large amount of abdominal fat is a risk factor for metabolic changes, such as type 2 diabetes mellitus, cardiovascular diseases, atherosclerosis, and acute myocardial infarction [38]. Other complications of fat accumulation and consequent obesity are insulin and leptin resistance. In fact, several recent studies have linked behavioral changes with obesity and resistance of the brain to these two hormones, both of which can cross the blood-brain barrier and have receptors in important areas, such as the hippocampus and hypothalamus [39-42].

Behavioral tests in the present study revealed that animals fed a cafeteria diet had a different response to risperidone. The animals were exposed to this diet during lactation and post-lactation, which are critical phases in the formation of important brain structures, such as the cortex, hippocampus, and amygdala [43]. Furthermore, the diet was administered long enough to generate long-term deleterious effects.

Some studies have already shown that palatable diets can attenuate anxiogenic states originating from stressors in the pre- and postnatal stages in rodents [44]. The cafeteria diet promoted a similar anxiolytic effect in the present study, as the CAF-S group presented a higher number of entries into and time spent in the center of the OF, as well as the highest mean number of entries into the open arms of the EPM, although without statistical significance. Macedo, Medeiros [45] suggested that ingestion of tryptophan-rich foods, such as peanuts and chocolate, may stimulate the serotoninergic system, promoting a decrease in anxiety.

Kaminska and Rogoz [25] reported that risperidone (0.1 mg.kg^{-1}) had an anxiolytic effect, as measured using the EPM. We observed this in the CTRL-R group in the present study. This effect may be caused by risperidone-mediated antagonism of 5-HT$_{2A}$ receptors located in pyramidal glutamatergic neurons and GABAergic interneurons in the cortex and hypothalamus regions.

Importantly, the EPM and OF test results in the present study showed that risperidone had different effects on anxiety between CTRL and CAF groups. In the EPM test, the time spent by CAF-R group animals in the open arms did not differ from that of the CAF-S group

Table 2
Number of social interactions and time spent for each male offspring social behavior on D118 (n = 10–11).

Variables	CTRL-S	CTRL-R	CAF-S	CAF-R
	Number of social interactions			
Anogenital	6.75 ± 2.68^{a}	5.20 ± 0.80^{a}	2.00 ± 0.57^{a}	4.40 ± 1.21^{a}
Body	13.00 ± 1.68^{a}	10.04 ± 1.16^{a}	8.00 ± 1.00^{a}	12.40 ± 1.57^{a}
Snout	3.75 ± 1.03^{a}	4.00 ± 1.58^{a}	1.67 ± 1.20^{a}	2.80 ± 0.80^{a}
Mount/roll	1.75 ± 1.43^{a}	2.60 ± 0.81^{a}	0.33 ± 0.33^{a}	1.00 ± 0.44^{a}
	Time spent (s)			
Anogenital	27.31 ± 2.16^{a}	21.52 ± 4.76^{ab}	6.81 ± 2.93^{b}	12.16 ± 3.88^{b}
Body	58.96 ± 11.19^{a}	32.38 ± 3.89^{a}	43.23 ± 7.20^{a}	35.02 ± 6.50^{a}
Snout	10.15 ± 4.53^{a}	9.40 ± 3.64^{a}	5.55 ± 3.69^{a}	5.41 ± 2.56^{a}
Mount/roll	4.69 ± 2.70^{a}	9.11 ± 2.55^{a}	1.51 ± 1.00^{a}	1.78 ± 0.84^{a}

Control saline (CTRL-S); Control risperidone (CTRL-R); Cafeteria saline (CAF-S); Cafeteria risperidone (CAF-R). Different letters between the lines indicate a statistically significant difference by the Newman Keuls test ($p < 0.05$).

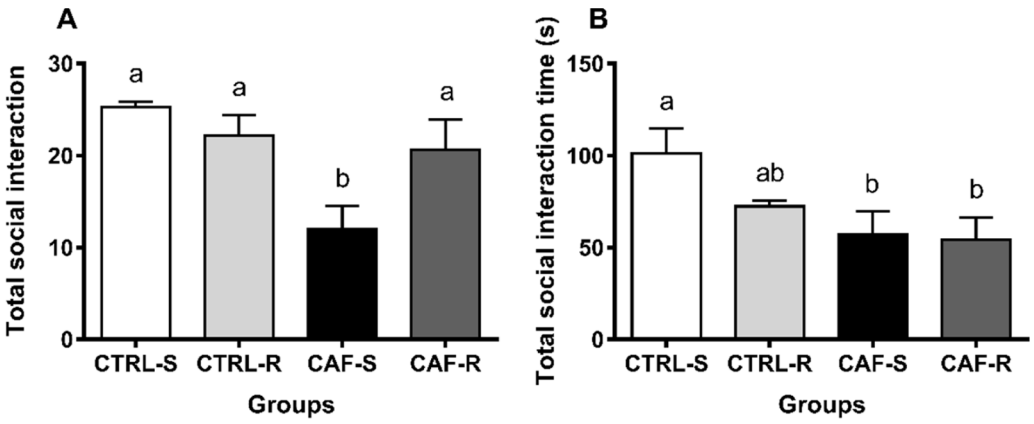

Fig. 4. Total social interaction (A) and time of total social interaction (B) in interaction social test on D118 (n = 10–11). Legend: Control saline (CTRL-S); Control risperidone (CTRL-R); Cafeteria saline (CAF-S); Cafeteria risperidone (CAF-R). Different letters between the columns indicate a statistically significant difference by the Newman Keuls test ($p < 0.05$).

Table 3
Redox state of the brain (prefrontal cortex and hippocampus) of the male offspring in adulthood on D120 (n = 8).

Variables	CTRL	CAF
	Prefrontal cortex	
Malondialdehyde (nmol/mg protein)	11.72 ± 1.24[a]	10.75 ± 0.44[a]
Carbonylated protein (nmol/ml)	24.81 ± 6.27[a]	29.06 ± 8.31[a]
Superoxide dismutase (U SOD/mg protein)	83.36 ± 2.77[a]	100.93 ± 8.01[a]
Glutathione S-Transferase (GST µmol/min/mg protein)	5.88 ± 0.42[b]	7.81 ± 0.35[a]
	Hippocampus	
Malondialdehyde (nmol/mg protein)	8.52 ± 0.78[b]	11.52 ± 1.04[a]
Carbonylated protein (nmol/ml)	29.47 ± 7.49[a]	34.00 ± 9.08[a]
Superoxide dismutase (U SOD/mg protein)	74.05 ± 2.77[b]	92.17 ± 8.01[a]
Glutathione S-Transferase (GST µmol/min/mg protein)	6.42 ± 1.08[a]	4.96 ± 0.88[a]

Control (CTRL) and Cafeteria (CAF). Different letters on the same line indicate significant difference by the Newman Keuls test ($p < 0.05$).

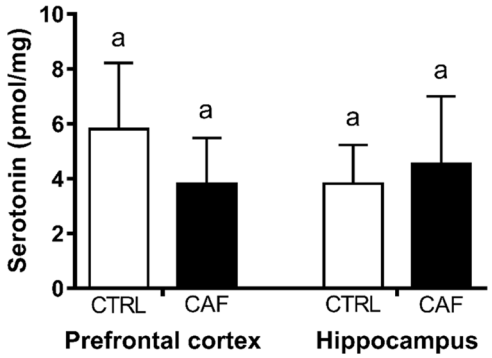

Fig. 5. Serotonin levels of the brain of male offspring on D120 (n = 8). Legend: Control (CTRL) and Cafeteria (CAF). Different letters between the columns indicate significant difference by the Newman Keuls test ($p < 0.05$).

animals. However, the CTRL-R group animals spent more time in the open arms than the CTRL-S group animals. In the OF test, the number of entries into and time spent in the center was lower in the CAF-R group than in the CAF-S group; however, the number of entries and time spent did not differ between the CTRL-R and CTRL-S groups.

Rodents have a natural tendency to explore new environments to collect information and spatial mapping. Such behavior can be stimulated by changes in the anxiety/fear levels or impulsivity of the animals. Spatial memory, governed by the hippocampus, is directly associated with how much these animals move in the OF arena, since it is by exploration that rodents acquire information about their new environment [46]. Marwitz et al. [47] treated rats with a cafeteria diet for 10 weeks and obtained results similar to those of the present study, namely increased locomotion. This observation indicates that hypercaloric or palatable diets do not result in decreased locomotion in rodents, even when weight and adipose tissue are increased [48]. Thus, because they had lower anxiety than animals on a standard diet, the CAF-S group increased their exploration in a new environment such as the OF.

McOmish et al. [49] reported a reduction in the locomotion of mice who received 0.4 mg.kg^{-1} of risperidone intraperitoneally, similar to that observed in the CTRL-R and CAF-R groups of the present study, who covered smaller distances in the OF test. Atypical antipsychotics, such as risperidone, are used to treat schizophrenia, with the aim of reducing hyperactivity. As such, the drug may cause some decreases in locomotion. Although risperidone decreased locomotion in both the CTRL-R and CAF-R groups, the amplitude of this decrease differed. We observed that the CAF-R group showed 10-fold lower locomotion than the CAF-S group, whereas in the CTRL-R group, locomotion was only 2.5-fold lower than in the CTRL-S.

The NOR test is based on access to novelty. It stimulates the animal to approach the new object. Animals have an innate preference for exploring novel objects over familiar objects, and this preference may be affected by neurotransmitter alterations caused by pharmacological agents [50, 51]. Furthermore, the NOR test can be considered a model for evaluating episodic memory in rodents, which is directly related to the circuit generated in the CA1 region of the hippocampus and in the medial prefrontal cortex [52]. The hippocampus is susceptible to high-energy intake dietary changes. Hypercaloric diets may generate metabolite accumulation that can increase the oxidative stress and neuroinflammation states in the hippocampus, resulting in memory impairment [22, 53]. The CAF-S group showed no preference for the novel object in the NOR test, indicating that the cafeteria diet may have compromised these animals' episodic memory.

In an animal model of Alzheimer's disease, Wuet al. [54] administered high doses (2.0 and 4.0 mg.kg^{-1}) of risperidone over long periods of time. They reported memory improvements in the NOR test. We did not observe this effect of risperidone in the present study: the CAF-R group animals did not present longer exploration time of the novel object, and the exploration time of both objects was decreased, which may indicate a decrease in interest or recognition of the objects.

Anogenital interaction is an important behavior related to the investigation of a new individual of the same species, and it is a key component of social recognition [55, 56]. Zilkha et al. [57] evaluated the effects of a high-fat diet on social behavior in a model of autism (BTBR mice). The high fat diet (60% kcal in fats), which was administered from weaning to the age of 9 weeks, led to an even greater decrease in the interaction of the animals, and this behavior was classified as a high degree of autism.

In the present study, the cafeteria diet caused a decrease in the number and total time of social interactions in these animals. Furthermore, the anogenital interaction results suggested that the

cafeteria diet-fed animals had a decreased interest and recognition of other individuals of the same species, and that they may even have had decreased sexual interest [56]. However, risperidone administration had different behavioral effects, depending on the animal's diet. The number of total social interactions in the CAF-R group was higher than in the CAF-S group.

Western diets, especially those rich in fats, are promoters of ROS formation. Chronic ingestion of such diets favors oxidative stress in brain tissue, thus promoting damage to the synapses, mitochondrial dysfunction, and even neuronal death [11, 58]. Elevations of GST and SOD levels in the prefrontal cortex and hippocampus may indicate that a compensation mechanism has been created to prevent oxidative stress in these tissues. Intense ROS production in the body stimulates the production of higher concentrations of antioxidant enzymes to prevent imbalances of the redox state. MDA is a by-product of lipid peroxidation, which occurs when ROS interacts with membrane phospholipids. High MDA concentrations in the hippocampus indicate interference with cellular functions, neurogenesis, and thus with memory and learning, which are the primordial functions of this region [59]. It follows that the different behaviors observed in the tests performed by the animals may be related to alterations in the redox state of the prefrontal cortex and hippocampus

Serotonin is a monoaminergic neurotransmitter synthesized mainly in the neurons of the raphe nucleus. It regulates cognition, attention, emotion, pain, sleep, and excitation. Changes in serotonin signaling may trigger a number of neuropsychiatric disorders, such as schizophrenia, affective disorders, anxiety, and autism [60]. In particular, tissue oxidative stress is related to changes in serotonin signaling. It may decrease the production of rate-limiting enzymes in the synthesis of this neurotransmitter, such as tryptophan hydroxylase [61].

Evaluations of brain tissue redox state in the present study indicated that the CAF groups had mainly developed a state of oxidative stress in the hippocampus. Although there were no differences in serotonin levels between the hippocampus and prefrontal cortex of the CAF animals, it is still possible that alterations in other pathways of serotonin signaling were compromised. This would explain the different responses caused by risperidone in the behavioral tests.

Recent work has shown that obesogenic diets may cause changes in dopamine receptors and consequently in sensitivity to dopaminergic drugs [62–65]. Risperidone has a high affinity for 5-HT_{2A} receptors, effectively blocking them. It also stimulates 5-HT_{1A}, and has lower antagonist activity on dopamine D_2 receptors [66]. Interaction between the prefrontal and hippocampal cortices is important for many behavioral and cognitive processes involving serotonergic receptors, such as 5-HT_{2A} and 5-HT_{1A} [66]. Therefore, the present results constitute a new viewpoint on how obesogenic diets affect sensitivity to drugs with serotonergic targets.

The present study has a few experimental limitations. First, we utilized the same animals to perform both the EPM and social interaction tests. Although the results presented indicate a clear change in the sensitivity of risperidone in both tests for the cafeteria diet group, an ideal experimental situation would include performing each test with naive animals or even with half of the animals performing the EPM test first while the other half perform the social interaction test, to counterbalance the animals of all groups. Second, we used only one dosage of risperidone, which was chosen according to the existing literature [23–25]; however, as the drug acts in a dose-dependent manner [67, 68] tests with different dosages must be performed with the model proposed in this work to better understand the changes in drug sensitivity. Finally, although the body weights of CAF offspring at the time of weaning were lower than that of CTRL, the difference was not statistically significant. However, this may have influenced the behavioral outcomes. Future studies using each phase separately (lactation and post-weaning) are necessary to assess the impact of this result.

In summary, the model proposed in the present study showed that the diet consumed by the offspring can alter behavior and affect sensitivity to serotoninergic drug involved in that behavior. This fact corroborates recent research showing that oxidative stress in brain tissues may alter the signaling of some neurotransmitters. It also calls attention to the use of central-acting drugs animals with obesogenic diets.

5. Conclusions

The cafeteria diet caused increased locomotion, had anxiolytic effects, generated a memory deficit, and affected social interaction in animals that were fed it from lactation. Risperidone administered to animals on a cafeteria diet led to a greater reduction in locomotion, had an anxiogenic effect, caused impaired memory, and improved social interaction.

The behavioral alterations observed in the CAF group that received risperidone may have been related to oxidative stress in the hippocampus and prefrontal cortex, and they may also have affected the encephalic serotoninergic system.

Disclaimer statements

Contributors: all of the authors contributed equally.

Declaration of Competing Interest

The authors report no conflicts of interest.

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