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Differential effects of high-sucrose and high-fat diets on metabolic syndrome, BBB integrity, and hippocampal Aβ accumulation

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Abstract

Metabolic syndrome (MS) is a global health problem and a recognized risk factor for cognitive impairment and Alzheimer's disease (AD), but the different effects of specific dietary components on MS-related neurological damage remain unclear. This study investigated the effects of long-term high-calorie diets on metabolic parameters, blood-brain barrier (BBB) integrity, and hippocampal β-amyloid (Aβ) accumulation. Male Wistar rats were fed a control diet, a high-sucrose diet (HSD, 30% sucrose in drinking water), or a high-fat diet (HFD, 30% lard) for 12 months. The study assessed metabolic syndrome parameters, spatial memory (Morris water maze), BBB permeability (Evans blue staining), tight junction proteins (ZO-1, Occludin), and the levels of Aβ and its transporters (LRP1, RAGE). The results showed that both HSD and HFD induced central obesity, increased BBB permeability, and spatial memory deficits in rats; however, disruption of the blood-brain barrier was not associated with changes in tight junction protein expression. Notably, hippocampal Aβ accumulation increased only in the high-fat diet group (HFD group) after 8–12 months, associated with a significant downregulation of the Aβ clearance receptor LRP1, while no changes were observed in RAGE. In contrast, the high-fat diet group (HSD group) exhibited more extensive metabolic syndrome-related alterations, including hyperglycemia and hypertension. Our results suggest that while both sucrose- and fat-based high-calorie diets impair the integrity of the blood-brain barrier and cognitive function, only high-fat intake promotes hippocampal Aβ accumulation by downregulating LRP1. These results suggest that although both dietary patterns contribute to metabolic syndrome and cognitive impairment, high-fat intake may pose a more specific risk to Alzheimer's disease pathology.

Keywords: Beta-amyloid peptide, Blood-brain barrier dysfunction, Hypercaloric diets, Metabolic syndrome, Obesity, Spatial memory alteration.

1. Introduction

Metabolic syndrome (MS) is one of the main health problems worldwide, which is considered an epidemic because of its increased prevalence [1]. MS is defined as the simultaneous presence of at least three out of five metabolic alterations, like central obesity, hyperglycemia, hyperinsulinemia, hypertension, and dyslipidemia, including hypertriglyceridemia and hypercholesterolemia. Each of these metabolic alterations may increase the risk for the development of cardiovascular diseases and Type 2 diabetes [2].

The metabolic alterations accompanying MS may induce damage to the macro and microvasculature, including those present in the central nervous system (CNS) [3], which is called vascular dysfunction and is associated with the development of cognitive impairment and neurodegenerative diseases such as Alzheimer's [4-7].

The blood-brain barrier (BBB) in the CNS microvasculature is constituted by astrocytes, pericytes, and endothelial cells; these components are responsible for tightly regulated transport of substances like nutrients, ions, and toxic compounds from circulation to the brain and vice versa. This transport occurs through cells by active transport or between cells by modifying permeation of tight junctions [8, 9].

Metabolic syndrome may increase the BBB permeability to damaging molecules and pro-inflammatory cells to the brain, favoring neuronal damage [10, 11]; however, the mechanism explaining these relations is still mater of research.

The accumulation of amyloid-beta (Aβ) peptide in the brain is considered one of the causes for the development of Alzheimer's disease (AD) [12]. This peptide is produced in the brain by a strictly regulated pathway and cleared by active transport in a coordinated way by the low-density lipoprotein receptor-related protein-1 (LRP1) and the receptor for advanced glycation end products (RAGE).

Although MS is considered a risk factor for BBB dys-

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function and AD establishment, the role of the MS-associated alterations, for example, central obesity, hypertension, hyperglycemia, dyslipidemia, as well as the kind of caloric source, is not well established. Furthermore, our research aimed to analyze the pathological profile of the MS induced by chronic consumption of hypercaloric diets from carbohydrates or fat sources and its effect on BBB integrity and Aβ accumulation in rats' hippocampi.

2. Material and methods

2.1. Reagents

Primary and secondary antibodies were purchased from Santa Cruz Biotechnology (Dallas, Texas, USA) and Bio-Rad (Hercules, California, USA), respectively. Unless another source was described, all remaining chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.2. Diets

Twenty-one-day-old male Wistar rats were purchased from the Production, Care and Animal Experimentation Unit (UPCEA), Juarez Autonomous University of Tabasco.

Rats were randomly divided into three groups: The control group (Ctrl) that were fed with chow and tap water; the high sucrose diet group (HSD) was fed with chow and 30% sucrose in substitution of drinking water, and the high-fat diet group (HFD) that was feed with home-made chow supplemented with 30% of fat (lard) and tap water. Rats were maintained in a 12-h light/dark cycle with a controlled room temperature of 25°C and free access to food and water for 12 months. Detailed composition and calories consumed in diets were published previously [13]

2.3. Bodyweight and metabolic syndrome-related parameters

Rats were weighed monthly to evaluate their weight gain. Blood pressure (systolic, diastolic, and medium (MBP) was monitored with the small animal tail noninvasive blood pressure system (NIBP 200A of Biopac System, Inc.). Blood samples were obtained from the rat's tag for the analysis of biochemical parameters such as serum glucose, cholesterol, triglycerides, LDL, and HDL, which were measured in a Selectra Pro XS using conventional colorimetric methodologies.

2.4. Spatial memory evaluation

For the memory test, we used the Morris water maze protocol. Briefly, a metallic 1.8m diameter pool was filled with 60 cm of 24°C water (depth). The pool was divided into four quadrants. In one of them, a circular acrylic platform was submerged at 1 cm below the water level, and one visual reference was placed in each quadrant. For the four-day-long adaptation phase, rats were placed every day in the opposite quadrant to the platform and were allowed to search freely for the platform for 90 seconds; if the rat did not find the platform, it was manually placed on and left for 30 seconds. On the fifth day, the visual reference was removed, and the experiment was repeated in the same way; rats were permitted to search for the platform for a maximum of 120 seconds. All procedures were recorded with EPCOM video camera. Latency time was calculated as the time rats spent in the quadrant where the platform was located in the previous adaptation phase.

2.5. Blood-brain barrier permeability

After eight, ten, or twelve months of diet consumption, each rat received an injection with 2% Evans blue solution in PBS at (100µl/kg) through the carotid artery, which was left in circulation for 90 minutes; after that, animals were perfused transcardially with 100 mL of PBS before 100 mL of 4% paraformaldehyde in PBS.

At the end of perfusion, the hippocampus was dissected and stored in formamide for 20 hours at -80°C. Finally, samples were centrifuged at 250 x g for 60 min before measurement of absorbance of the supernatant at 610 nm in a microplate reader.

2.6. Western blot

Hippocampus simples were homogenate mechanically in 100µl of RIPPA lysis buffer supplemented with protease inhibitor cocktail before being sonicated (amplitude of 80%) for one minute with 30 pulses and centrifuged at 10,000 x g for 10 minutes at 4°C. The supernatant was collected, the protein concentration in samples was quantified by the Bradford method, and samples were mixed with 5X loading buffer (glycerol 30%, SDS 10%, Tris 0.5 M, bromophenol blue 0.01%, and β-mercaptoethanol) at a concentration of 4µg/µl and warmed up at 95 °C for 10 min. After being separated by electrophoresis in 12% SDS-PAGE gels, proteins were transferred to PVDF membranes that were blocked for 2h at room temperature with constant shaking in a 2% solution of free fat milk in washing buffer (NaCl, Tween 20, Tris, SDS).

After washing three times 10 min., membranes were incubated overnight with the primary antibodies diluted 1:1000 in washing buffer added with 3% of BSA (goat anti-ZO-1, rabbit anti-Occludin, goat anti-amyloid beta, rabbit anti-LRP1, rabbit anti-RAGE, and mouse anti-GAPDH as a loading control).

The next day, membranes were washed out and incubated with the HRP-conjugated secondary antibodies diluted 1:10000 for the chemiluminescent detection using an Immobilon Western AP chemiluminescent substrate (Millipore, Bedford, MA, USA).

2.7. Determination of tight junction proteins by PCR

Total RNA was extracted using the TRIzol reagent according to the manufacturer's standard protocol. Complementary DNA (cDNA) was then synthesized from the extracted RNA using the Thermo Scientific RevertAid First Strand cDNA Synthesis Kit (#1622), following the provided instructions. The tight junctions proteins' expression was analyzed by qPCR; the following primers were used: ZO-1 5′-ACAGGTAGGACAGACGATCA-3' - 5′-TCAGCAGCAACAGAACCAG-3'; Ocludin 5′-TGTCTCTAGGTTATCGTTGCTG-3' - 5′-CTTTGTATAAGTCACCGCCTCT-3'; and Claudin 1, 5′-GCACTTCATCATCTTCTAAGCAC-3' - 5' TTCGACTCCTTGCTGAATCTG-3'. GAPDH was used as housekeeping gene 5′-TCTCTGCTCCTCCCTGTTC-3' - 5'- GTAACCAGGCGTCCGATAC-3'.

2.8. Statistical analysis

Results were analyzed using a one-way ANOVA and Dunnett's posthoc test for the comparison between experimental groups versus the control group; in all cases, the difference was considered significant at a p-value < 0.05.

3. Results

3.1. Obesity and metabolic syndrome parameters

The consumption of both hypercaloric diets induced central obesity (measured as retroperitoneal fat) without being overweight after six months (Data not shown); however, other characteristics associated with metabolic syndrome (MS) changed only after eight months; therefore, our results are reported starting at eight months of diet consumption.

Table 1 shows that, besides retroperitoneal fat, only glucose increased in the HSD and mean arterial pressure (MAP) in HFD. At the tenth month, retroperitoneal fat, glucose, systolic and MAP blood pressure increased for both experimental groups HSD and HFD; additionally, the mean value for triglycerides increased but without significant difference (128±37 for Ctrl vs 181±46 for HSD and 154±32 for HFD) this disconcerting result is probably because of a big dispersion of data; until this point, we can consider the HSD and HFD rats as MS because the developed obesity, hyperglycemia and hypertension. After 12 months of diet consumption, values are similar to those for 10 months; however, the systolic blood pressure of the control group increased from 104 and 94 mmHg at eight and 10 months to 126 mmHg, with the consequent loss of significance against the experimental groups that kept

high values of systolic pressure (Table 1). The increase in blood pressure may be the result of normal aging in rats.

3.2. Functional damage

Our results show that after eight and twelve months of diet consumption, latency values decreased in rats subjected to both hypercaloric diets (Figure 1A); that means the spatial memory was affected, although the animals did not develop metabolic syndrome at eight months (HSD group developed higher central obesity and hyperglycemia; whereas HFD developed central obesity with higher MBP). Additionally, the Blood-Brain barrier (BBB) suffered integral damage identified as increased EB crossing from circulation to the brain in rats of both groups after 10 and 12 months of diet (Figure 1B) but not at 8 months.

3.3. Tight junctions' components

In order to analyze structural modifications that explain the increase in EB migration from circulation to the brain, we determined the main gap-junction forming proteins

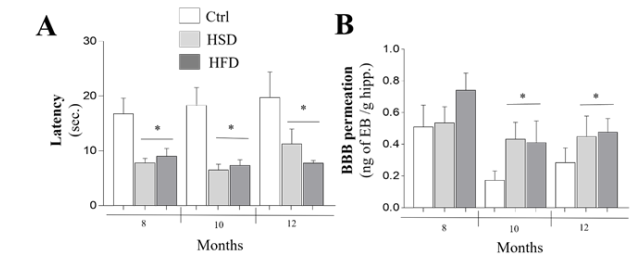


Fig. 1. Changes in Memory and BBB integrity result from chronic consumption of hypercaloric diets. Panel A shows the latency time after eight, ten, and twelve months of diet consumption; Panel B shows the amount of EB that crosses the BBB. For all experiments, n=6; *p<0.05 vs Ctrl group.

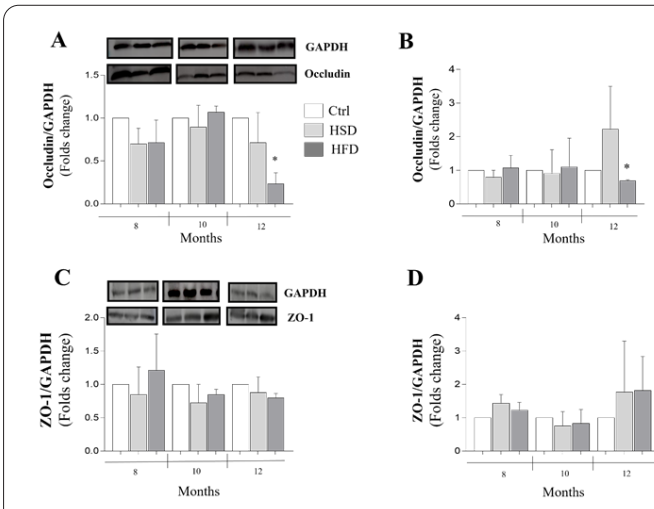


Fig. 2. Analysis of tight junctions' components. Changes in the expression of Occludin and ZO-1 were evaluated by Western blot (WB) and RT-PCR. Panel A shows the result of Western blots for Occludin and a representative image, whereas Panel B shows the result of PCR analysis of the same protein. Panels C and D show the results of western blot and PCR for the expression of ZO-1, respectively. For western blot experiments, n=3; whereas for PCR experiments, n=4, *p<0.05 vs Ctrl group. WB and PCR expression were analyzed using GAPDH as internal control, and results were normalized with a 1 to Ctrl group value.

Table 1. Analysis of biochemical and zoometric parameters associated with metabolic syndrome.

	8 months			10 months			12 months		
	Ctrl	**HSD**	**HFD**	**Ctrl**	**HSD**	**HFD**	**Ctrl**	**HSD**	**HFD**
Body weight (g)	537 ± 5	583 ± 29	505 ± 48	555 ± 43	519 ± 48	552 ± 30	582 ± 35	654 ± 23	591 ± 88
Retrop. Fat (% body weight)	1.9 ± 0.7	**3.2 ± 0.5***	**5.2 ± 1.8 ***	1.5 ± 0.1	**3.7 ± 1.2 ***	**5.4 ± 0.9 ***	2.3 ± 0.4	**4.9 ± 2.1 ***	**6.3 ± 1.3 ***
Glucose (mg/dL)	130 ± 10	**150 ± 11***	131 ± 7	118 ± 3	**137 ± 2***	**150 ± 14***	101 ± 10	122 ± 14	**129 ± 17 ***
Triglycerides (mg/dL)	153 ± 29	177 ± 34	**90± 25***	129 ± 37	**182 ± 46***	154 ± 32	124 ± 22	**197 ± 31***	108 ± 04
Cholesterol (mg/dL)	97 ± 9	**75 ± 9***	97 ± 7	85 ± 13	81 ± 18	88 ± 9	116 ± 17	84 ± 13	94 ± 24
HDL (mg/dL)	24 ± 2.1	23 ± 3.8	22 ± 1.2	21 ± 2.5	28 ± 8.5	25 ± 3.3	22 ± 2.8	21 ± 3	21 ± 6.0
LDL (mg/dL)	13.1 ± 3.7	8.4 ± 1.6	14.0 ± 3.0	12.0 ± 3.3	6.4 ± 1.3	7.6 ± 1.1	16 ± 4.1	7.3 ± 1.5	10.1 ± 3.5
SBP (mmHg)	104 ± 03	106 ± 10	115 ± 09	94 ± 04	**143 ± 30***	**131 ± 22***	126 ± 15	143 ± 15	135 ± 11
DBP (mmHg)	54 ± 07	52 ± 04	69 ± 15	69 ± 5	84 ± 17	92 ± 22	91 ± 19	112 ± 20	84 ± 11
MAP (mmHg)	71 ± 13	69 ± 4.7	**83 ± 10 ***	77 ± 4	**104 ±8 ***	**106 ± 19 ***	107 ± 17	**178 ± 28 ***	102 ± 11

The displayed parameters were quantified as described in the Materials and Methods section. Retrop. Fat= retroperitoneal fat; SBP= systolic blood pressure; DBP= diastolic blood pressure; MAP=mean blood pressure. Data in bold are significantly different vs the Ctrl group. The "n" value was 6 for all groups, except for Glucose for HSD 12 months, with a value=3. * = p<0.05 vs Ctrl.

Claudin, Occludin, and ZO-1. Figure 2 shows that Occludin (Fig. 2, panels A and B), measured by western blot and RT-PCR, diminished only after 12 months in the HFD, without changes in any other period or HSD group (Fig. 2, panels C, D, and E).

3.4. Amyloid beta, LRP, and RAGE receptors

Finally, an analysis of the transport through the BBB was made, focused on the Amyloid beta (Aβ) accumulation. The low-density lipoprotein receptor-related protein-1 (LRP1) and the receptor for advanced glycation end products (RAGE) located in endothelial cells of BBB were measured in the rat's hippocampi, in addition to the content of Aβ. Figure 3A shows that the Aβ increased in the HFD group from eight to twelve months, without significant changes in the HSD group. In contrast, in complete correlation, LRP1 protein decreased after ten and twelve months of the same diet, without changes in levels of RAGE (Fig. 3B and 3C).

4. Discussion

Obesity and metabolic syndrome (MS) are considered nowadays as the leading health problems because of their epidemic prevalence, as well as their strong association with the development of cardiovascular and neurodegenerative diseases [14, 15].

In previous work, we reported that rats subjected to the consumption of hypercaloric diets based on high sucrose content (30% in water) and high-fat diet (30% in solid chow) developed central obesity after six months, without the establishment of MS, but with a differential profile of metabolic alterations. Rats fed with the combined diets also developed central obesity with reduced growth, which was detected as a smaller size and body weight gain [16]. Based on those results, we subjected male rats to the HS and HF diet consumption for twelve months and discarded the combined diets for this study.

Metabolic alterations induced by hypercaloric diet consumption are well described with several animal models; however, the study of neurological damage caused by the pathologic changes associated with MS is limited. Also, a clear explanation for the differential influence or association of specific changes like central obesity, hyperglycemia, hypertension, and hypertriglyceridemia with neurological damage is still missing and was the goal of our research.

With this study, we demonstrated that after eight and until twelve months of consumption, either hypercaloric diets induced central obesity but with different metabolic alterations; i.e., at eight months, rats from the HSD group developed hyperglycemia, but the HFD group instead showed an increased MBP (mean blood pressure). Interestingly, sugars or fats can induce obesity with different metabolic alterations, as demonstrated before [17, 18]. At ten months, all the metabolic changes were similar between experimental groups, with central obesity (slightly higher than HFD), hyperglycemia, high mean values of triglycerides, and high systolic and mean blood pressure. These patterns changed for the 12 months, with the reestablishment of control values of triglycerides for the HFD group and an increase in systolic blood pressure for the Ctrl group, which may be a physiological process associated with age [19].

For the analysis of functional damage on CNS, the Morris water maze memory test was employed; as a result, both diets induced a reduction in latency time, translated as shortening of spatial memory, an essential CNS function regulated in the hippocampi [20]. On the other hand, these results were supported by the permeation to the Evans Blue (EB), an indicator for structural damage in the BBB [21]. Those results support the hypothesis that MS induces damage in the BBB, which is considered a link between MS and the development of neurodegenerative diseases like Alzheimer's. In line with our findings, Salameh et al. recently reported BBB dysfunction in a mouse model of type 2 diabetes induced by high-fat diet consumption [22]. Their results showed a downregulation of tight junction proteins like ZO-1 and Claudin-12, which was related to ROS generation.

Key components of the BBB that explain its high se-

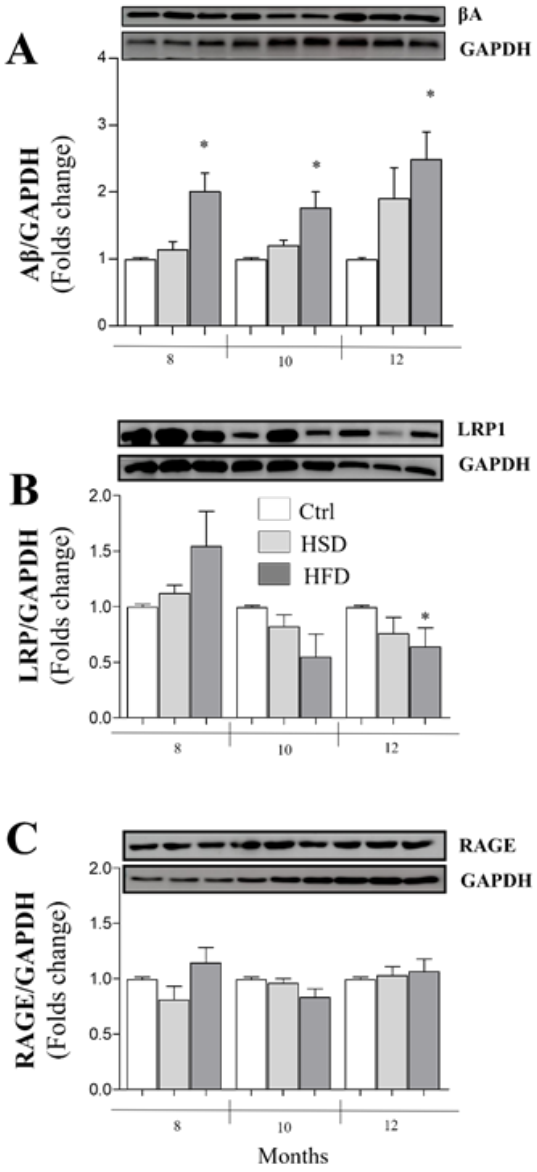


Fig. 3. Accumulation of AB in the hippocampus of rats. The content of amyloid β peptide (Aβ) and its transport-associated receptors LRP1 and RAGE were evaluated by western blot. Panel A shows the mean values of Aβ accumulated in the hippocampus of rats after 8, 10, and 12 months of diet consumption and a representative image. Panels B and C show the content of LRP1 and RAGE in the hippocampus of rats, with a representative image of the western blot. For experiments, n=3; *p<0.05 vs Ctrl group using GAPDH as an internal control; results were normalized with a 1 to Ctrl group value.

lectivity are the tight junctions, which join adjacent endothelial cells through specific proteins that are anchored in the cytoskeleton [23]. Some alterations in expression or function in tight junction proteins have been reported as part of neurological damage in patients with-, or models of neurodegenerative diseases [24]. Interestingly, we find a reduced expression of Occludin without changes in either ZO-1 or Claudins in the HFD group at 12 months of diet (Fig.2 and Supplementary). This result is very relevant considering that Occludin is an integral protein among Claudins are the most critical components with extracellular loops that regulate the vascular permeability [25]; however, its down-regulated expression does not explain the functional alterations found in eight or ten months in the HSD and HFD groups. These results indicated that in our models of MS, tight junctions' modifications are not strongly associated with endothelial dysfunction; similar results were also reported by Contu et al. [26]. Additionally, it is important to consider post-transcriptional regulator factors for these proteins, like phosphorylation [27], which was not analyzed but remains an attractive response.

An additional pathway for the increased permeation of BBB is defective transport through endothelial cells [9]. A critical role of the highly regulated transport in CNS is the clearance of amyloid β (Aβ), one key factor for the setting up of Alzheimer's Disease (AD), which transport between circulation and brain is regulated mainly by the low-density lipoprotein receptor-related protein-1 (LRP1) and the receptor for advanced glycation end products (RAGE); both are located in endothelial cells of BBB. A significant accumulation of Aβ was observed in the hippocampus of the HFD group, in complete agreement with the BBB permeation and spatial memory alteration (Fig. 1). It may be associated with the downregulation of LRP1 after ten and twelve months of diet (Fig. 3). The defective expression of this receptor in the endothelium is related to Aβ accumulation and with the prevalence of AD either in patients and animal models [28].

As it was reported previously, consumption of diets with a high content of fat downregulates the expression of LRP1 through different mechanisms: The brain insulin resistance, induced by consumption of HFD, decreases PI3K-Akt signaling, which limits transportation of LRP1 to the cell membrane and therefore, the Aβ elimination [29]. Additionally, the consumption of HFD overregulates the expression of pro-inflammatory cytokines like IL-1β and TNF-α, which downregulates LRP1 transcription by activating NF-κB [30, 31]. On the other hand, the increased expression of influx transporters of Aβ, like ABCB1, simultaneously with the presence of ApoE4 isoform, may enhance its intracellular accumulation [32]. All together, these mechanisms explain how HFD endangers LRP1 function and associated pathways, leading to an increased Aβ accumulation and cognitive deterioration.

Based on our results, the effect of unbalanced diet consumption on the production or elimination of amyloid beta peptide, as well as a deeper analysis of BBB integrity under this metabolic background, seems as attractive goals for future research.

Our results indicate that metabolic syndrome induced by consumption of hypercaloric diets from different sources (sucrose or fat) has the same harmful effect on BBB permeation, independently of changes in the structural proteins related to tight junctions, as well as spatial memory shortening. Interestingly, the BBB permeation occurs when biochemical parameters are modified simultaneously: central obesity, hypertension, hyperglycemia, and hypertriglyceridemia were present in the HSD and HFD groups after ten months of diet consumption, suggesting that permeation may be a result of an additive effect but independent of tight junctions. On the other hand, accumulation of Aβ was stimulated only by HFD consumption with an inverse correlation with LRP1 expression, which may indicate that excessive fat consumption has a stronger effect on the establishment of Alzheimer's conditions than a carbohydrate-rich diet consumption, even though both drive to obesity.

Limitations of the study

Our results were obtained from a rodent model of chronic consumption of unbalanced diets and their effects on pathological indicators. Although the rats developed metabolic syndrome, this is not a model of dementia or even Alzheimer´s disease; however, our results cannot be extrapolated to similar human conditions and the link between consumption of unbalanced diets and cognitive impairments must continue to be analyzed.

Conflict of interest

The authors declare no conflict of interest.

Consent for publications

All authors have read and approved the final manuscript for publication.

Ethics approval

The experimental design complied with international and national regulations for the use of animals in research (Norma Oficial Mexicana NOM-062-ZOO-1999, technical specifications for production, use, and care of experimental animals) and was approved by the Institutional Committee for Ethics in Research from the Juarez Autonomous University of Tabasco.

Availability of data and material

The authors declare that they embedded all data in the manuscript.

Authors' contributions

CFA-G, NPG-C and EM-A participates in design the research idea; CFA-G, NPG-C, EM-A and ENC-H participates in doing the experiments, analyzing data and writing the manuscript.

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Use of artificial intelligence tools

Some sentences in this manuscript were revised with the assistance of artificial intelligence, based language models to improve clarity and readability. All intellectual content, interpretations, and conclusions are solely the responsibility of the authors.

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