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Haloperidol aumenta a peroxidação lipídica hepática promovida por uma dieta rica em gordura em ratos

Haloperidol increases hepatic lipid peroxidation promoted by high-fat diet in rats

El haloperidol aumenta la lipoperoxidación en tejido hepático promocionada por una dieta alta en grasas en ratas

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Resumo

Este estudo teve por objetivo avaliar os efeitos do tratamento com haloperidol (HAL) associado a uma dieta rica em gordura (DRG) sobre danos hepáticos e renais, níveis intracelulares de magnésio (Mg2+) e níveis de gordura abdominal. Ratos Wistar machos jovens foram alimentados com DRG ou dieta controle por 48 semanas e, na 24º semana, parte dos animais começou a ser co-tratada com HAL (1 mg/kg/dia por via intramuscular). Após 4 semanas da administração do HAL, os ratos foram eutanasiados e seus fígados e rins foram removidos para as análises. Os resultados mostraram que a DRG aumentou significativamente a peroxidação lipídica no tecido hepático dos animais, quando comparados aos animais tratados com dieta controle (P <0,05). Além disso, a associação entre DRG e HAL potencializou a lipoperoxidação no fígado dos animais (P <0,05). Por outro lado, a DRG e/ou HAL não promoveram alterações significativas nos níveis renais de lipoperoxidação. Encontramos uma correlação negativa entre os níveis intracelulares de Mg2+ e o conteúdo de gordura abdominal em todos os animais. Em conclusão, os dados apresentados sugerem interações adversas entre HAL e DRG no fígado. Além disso, a correlação negativa entre os níveis intracelulares de Mg2+ e o conteúdo de gordura abdominal, indica um possível envolvimento de Mg2+ no desenvolvimento da síndrome metabólica associada a uma DRG.

Palavras-chave: Haloperidol; Magnésio intracelular; Dieta hiperlipídica; Estresse oxidativo; Peroxidação lipídica.

Abstract

This study aimed to evaluate the effects of the treatment with haloperidol (HAL) associated with a high-fat diet (HF) on hepatic and renal damage, intracellular magnesium (Mg2+) levels, and abdominal fat content. Young male Wistar rats were fed with high-fat diet or control diet during 48 weeks and, at the 24-week, part of animals began to be co-treated with HAL (1 mg/Kg/day intramuscularly). After 4 weeks of the drug administration, the livers and kidneys were removed for analyses. The results showed that HF diet significantly increased lipid peroxidation in the hepatic tissue of treated animals, when compared to animals treated with control diet (P<0.05). Moreover, HF associated with HAL further increased the hepatic lipid peroxidation levels (P<0.05). In contrast, HF and/or HAL did not promote significant changes in renal lipid peroxidation levels. We also found a negative correlation between intracellular Mg2+ levels and abdominal fat content among all animals. In conclusion, the data presented suggest adverse interactions between HAL and HF on liver. Furthermore, the

negative correlation between the intracellular Mg2+ levels and the abdominal fat accumulation suggest a possible involvement of Mg2+ in the metabolic syndrome development associated with a HF diet.

Keywords: Haloperidol; Intracellular magnesium; High-fat diet; Oxidative stress; Lipid peroxidation.

Resumen

Este estudio tuvo como objetivo evaluar los efectos del tratamiento con haloperidol (HAL) asociado con una dieta alta en grasas (DAG) sobre el daño hepático y renal, los niveles de magnesio intracelular (Mg2+) y los niveles de grasa abdominal. Para esto, se trataron ratas Wistar macho jóvenes con DAG o con dieta de control durante 48 semanas. En la semana 24, parte de los animales comenzaron a ser tratados conjuntamente con HAL (1 mg/kg/día por vía intramuscular). Después de 4 semanas de administración de HAL, las ratas fueron sacrificadas y sus tejidos fueron retirados para análisis. Los resultados indicaron que una DAG aumentó significativamente la peroxidación lipídica en el tejido hepático en comparación con los animales tratados con dieta de control (P <0.05). Además, la asociación entre DAG y HAL aumentó la lipoperoxidación en el hígado de los animales (P <0.05). Por otro lado, DAG y/o HAL no promovieron cambios significativos en los niveles de lipoperoxidación renal. Encontramos una correlación negativa entre los niveles intracelulares de Mg2+ y el contenido de grasa abdominal en todos los animales. En conclusión, los datos mostrados indican interacciones adversas entre HAL y DAG en el hígado. Además, la correlación negativa entre los niveles intracelulares de Mg2 + y el contenido de grasa abdominal indica una posible participación de Mg2 + en el desarrollo del síndrome metabólico asociado con una DAG.

Palabras clave: Haloperidol; Magnesio intracelular; Dieta alta en grasas; Estrés oxidativo; Peroxidación lipídica.

1. Introduction

There is a large body of evidence indicating that high-fat diets have been associated to several damage to mammalian health (Bisschop et al., 2001; Chen, 2003; Morgan et al., 2003), which promotes in non-obese rats, a lot of effects such as insulin resistance, dyslipidemia, hypertension and abdominal obesity. Taken together, these effects are an aggregate of metabolic risk factors for cardiovascular disease, type 2 Diabetes mellitus (DM), and metabolic syndrome (Axen, Dikeakos & Sclafani, 2003). In this context, people with low

cellular levels of magnesium (Mg2+) have been a higher risk for both, DM and the metabolic syndrome (Ford & Mokdad, 2003; Lopez-Ridaura et al., 2004; Nadler, 2004). Indeed, hypomagnesaemia, a frequent condition in patients with DM, can be involved in the development of inadequate metabolic control and in chronic problems of DM (Moram & Romero,2003), including the increase of plasmatic lipoproteins peroxidation in rats (Rayssiguier et al., 1993), oxidative stress and hypertension (Paolisso & Barbagallo, 1997; Paiva Sousa et al., 2020).

The increased production of reactive oxygen species (ROS) and the decrease of the antioxidant capacity also has been associated to high-fat diet intake, obesity, some neuroleptic drugs use, aging, and to the beginning and progression of DM and its complications (Folmer et al., 2003; Fachinetto et al., 2005; Greenwood & Winocur et al., 2005; Saiki et al., 2007; Salgueiro et al., 2016; Visgueira de Sousa et al., 2020). In fact, high-fat diet promotes oxidative stress in blood, brain, kidney and liver (Folmer et al., 2003; Fachinetto et al., 2005; Greenwood & Winocur et al., 2005; Saiki et al., 2007; Visgueira de Sousa et al., 2020). Besides, this diet may increase the vulnerability of dopaminergic neurons to toxic metabolic derived of haloperidol (HAL) metabolism, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]pyridinium) (HPP+), via increased levels of ROS and nitrogen species (RNS) (Choi et al., 2005).

HAL is a neuroleptic drug that belongs to the butyrophenones group. It has an antagonistic action through dopaminergic D2-receptors (Soudijn, Van Wijngaarden & Allewijn, 1967), widely used for the treatment of acute and chronic psychosis (Nechifor, 2008). Among other undesirable effects, the prolonged use of HAL is associated with metabolic side effects such as weight gain and endocrine disruptions (Lin et al., 2006; Andreazza et al., 2015). Furthermore, HAL treatment increases significantly the erythrocyte Mg2+ concentration in schizophrenic patients (Nechifor, 2008). Indeed, there are pharmacokinetic and pharmacodynamic interactions between psychotropic drugs and Mg2+, and existent data sustain the idea that an increase of erythrocyte Mg2+ is involved with the action mechanism of some psychotropic drugs (Nechifor, 2008).

There are many published works linking the adverse and toxic effects of HAL in central nervous system with the increased production of ROS in specific regions of the brain (Polydoro et al., 2004; Reinke et al., 2004; Fachinetto et al., 2005; Andreazza et al., 2015). However, literature data concerning the effect of HAL on renal and hepatic tissues are scarce. In line with this, our group has shown that HAL was able to lead to a decrease on hepatic GSH levels (Dalla Corte et al., 2008), without affect the other measured hepatic and renal

oxidative stress markers.

Taking into account the exposed, the present study was designed to test the hypothesis that the treatment with HAL associated with a HF could potentiate hepatic and renal injuries. Additionally, we investigated the effect of both HF and/or HAL on intracellular Mg2+ levels in order to establish a possible correlation between intracellular Mg2+ and abdominal fat under our experimental conditions.

2. Materials and Methods

Materials

Coomassie brilliant blue G and malondialdehyde (MDA) were obtained from Sigma (St. Louis, MO–USA). Mono- and dibasic potassium phosphate, acetic acid, orthophosphoric acid, tris buffer (tris (hydroxymethyl) aminomethane), hydrogen chloride, trichloroacetic acid and sodium chloride were obtained from Merck (Rio de Janeiro – Brazil). Potassium chloride, magnesium sulfate, zinc chloride, copper carbide and manganese sulfate were obtained from Vetec (São Paulo – Brazil). Wheat flour, cornstarch (Maizena ®), lard, eggs, chicken breast, soybean oil, sugar, soybean bran, wheat bran and bone flour were obtained from the local shops.

Experimental Model and Treatments

Animals were maintained and used in accordance to the guidelines of the Committee on Care and Use of Experimental Animal Resources, School of Veterinary Medicine and Animal Science of the University of São Paulo, Brazil. Male Wistar rats with 3 months old (270–320 g) were kept in Plexiglas cages in a room with controlled temperature (22ºC ± 3) and 12 hours light/dark cycle. Animals were divided into four experimental groups, with 5-7 animals each: normal fat-diet (CON), high-fat diet (HF), normal fat-diet plus haloperidol (HAL), and high-fat diet plus haloperidol (HF-HAL). Rats received food (HF or control diet) and water *ad libitum*. Diets were made up as in Table 1 and the rats were fed in small metal dishes just before the beginning of the dark cycle (night).

Table 1. Composition of the diets

Composition of the diets	High-fat diet	Control diet
	(g/Kg)	
Protein	75.00	76.00
Carbohydrate	483.00	765.00
Fiber	35.00	37.00
Fat acid saturated	125.00	8.00
Fat acid unsaturated	230.00	62.00
Salt mixture[1]	48.00	48.00
Caloric content (cal/g)	5.35	3.91

1 The salt mixture has the following composition (g/Kg): KCl, 96.3; MgSO4, 56.7; ZnCl2, 0.4; CuCO4, 0.7; MnSO4, 1.2; bonemeal, 449.0, salt light, 152.0. The values were retired from Andriguetto (1986).

Diets were prepared weekly, and stored at 4ºC. Rats were fed with high-fat diet during 48 weeks (12 months). The haloperidol was used in the last 24 weeks (6 months) of the experimental period. Haloperidol (haloperidol depot – Janssen – Cilag) was administrated at a dose of 38 mg/Kg, the equivalent of 1 mg/Kg/day of unconjugated haloperidol. The control groups were treated with vegetable oil as vehicle. Injections were given intramuscularly every 4 weeks for 24 weeks in a volume of 1 mg/Kg. Ketamine in the dose of 1 mL/Kg was injected intraperitoneally as anesthetic. After 4 weeks of the last administration of drug, all the rats were euthanized by decapitation.

Biochemical and Statistical Analysis

After 12 months of treatment, animals were anesthetized and euthanized by decapitation. The livers and kidneys were removed and homogenized 1/10 (w/v) in 10 mM Tris – HCl buffer, pH 7.4 and centrifuged (1800 g, 4ºC, 10 minutes). The supernatant was used for protein and lipoperoxidation determination.

Protein was measured by the method of Bradford (1976) using bovine serum albumin as standard. Lipid peroxidation was measured as thiobarbituric acid reactive substances (TBA-RS). TBA-RS were determined in tissue homogenates by the method of Ohkawa et al. (1979), in which MDA, an end-product of fatty acid peroxidation, reacts with thiobarbituric acid (TBA) to form a colored complex. MDA values were determined with the absorbance coefficient of the MDA-TBA complex at 532 nm = 1.56 x 105/cm/mmol. TBARS values were expressed as nmol MDA/ g of tissues.

Intracellular magnesium concentration was determined in the blood plasma. The blood samples were collected by heart puncture, put into heparinized tubes and centrifugated at 1500 rpm for 8 minutes. The plasma was discarded and the erythrocytes were diluted 1/100 with lantan chloride and the assays were done by atomic absorption in a Perkin Elmer® Atomic Absorption spectrophotometer.

Results were expressed as mean ± SEM. The effects of HF diet and HAL were analyzed by two-way ANOVA followed by Duncan's Multiple Range test for specific comparisons between means (SPSS for windows 8.0, SPSS 1998, Chicago, IL). Correlation coefficients were determined by linear regression analysis. Differences between groups were considered significant when $p < 0.05$.

3. Results

Body weight gain

During the 48 weeks of treatment, body weight gain in HF animals was not different when compared with animals treated with normal diet (521.43 ± 64.93 vs. 500.00 ± 55.67 g). However, after 24 weeks of HAL treatment, both normal fat-diet and high-fat groups that received HAL had a slight, but significant decrease in body weight as compared with their respective controls (Figure 1).

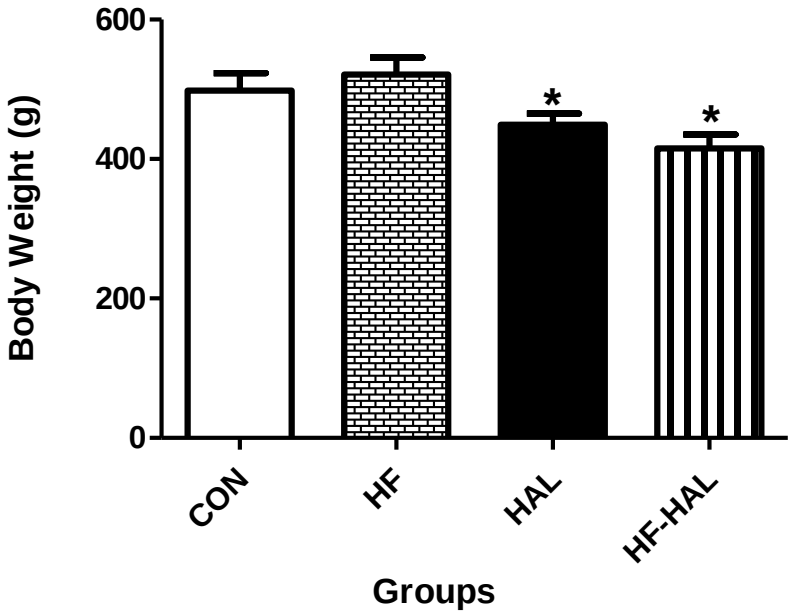

Figure 1. Rats body weight after 24 weeks of treatments. Animals were divided into four experimental

groups: normal fat-diet (CON), high-fat diet (HF), normal fat-diet plus haloperidol (HAL), and high-fat diet plus haloperidol (HF-HAL). Data are expressed as mean ± SEM for 5-7 animals per group. * p < 0.05.

Lipid peroxidation, Magnesium, and Abdominal fat index

The treatment with a high-fat diet caused a significant increase on hepatic lipoperoxidation levels as compared to animals that received a normal-fat diet (Figure 2). Additionally, HAL treatment was not able to cause any change per se on hepatic lipoperoxidation levels on normal fat diet-treated animals. In contrast, in high-fat diet treated animals, HAL potentiated lipid peroxidation in the liver (Figure 2). However, any difference was found among the groups concerning the renal lipoperoxidation levels, or intracellular Mg2+ levels (Data not show).

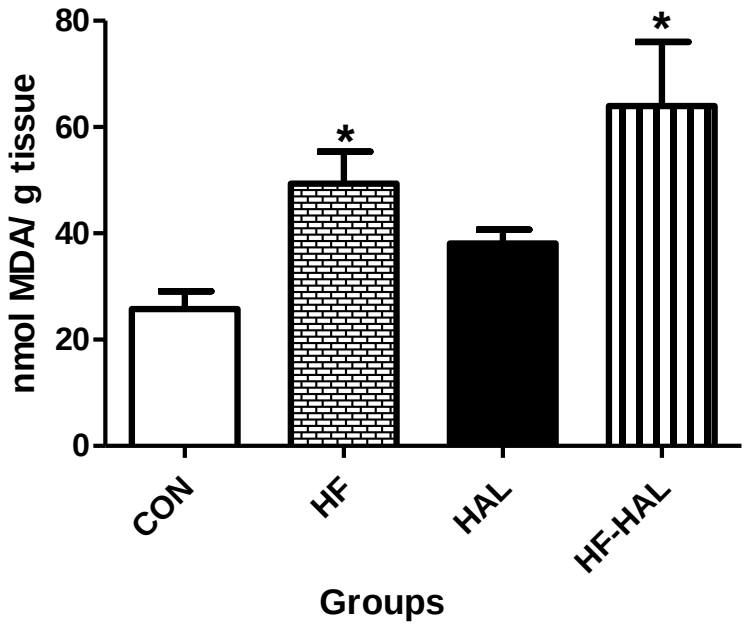

Figure 2. TBA-RS levels in rats' hepatic tissues. Animals were divided into four experimental groups: normal fat-diet (CON), high-fat diet (HF), normal fat-diet plus haloperidol (HAL), and high-fat diet plus haloperidol (HF-HAL). Data are expressed as mean ± SEM for 5-7 animals per group. * p < 0.05.

Treatments were not able to cause any change on intracellular Mg2+ levels or abdominal fat content (Figures 3A and 3B). Of particular importance, a statistically significant negative correlation was found between abdominal fat content and intracellular Mg2+ levels, when considered all groups (n=25; r = -0.594, p<0.01, Figure 4).

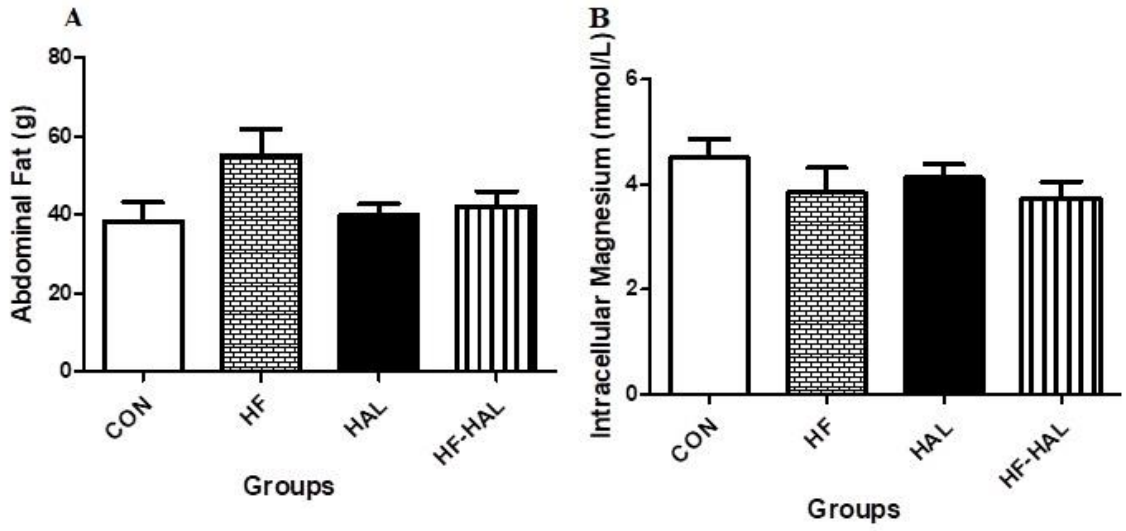

Figure 3. Abdominal fat content (A) and intracellular magnesium concentration (B). Animals were divided into four experimental groups: normal fat-diet (CON), high-fat diet (HF), normal fat-diet plus haloperidol (HAL), and high-fat diet plus haloperidol (HF-HAL). Data are expressed as mean ± SEM for 5-7 animals per group.

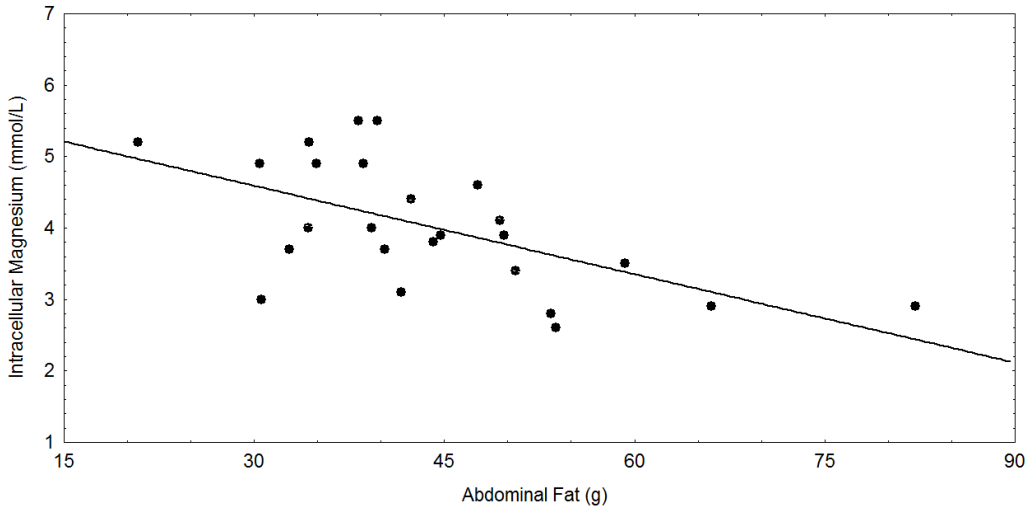

Figure 4. Correlation between abdominal fat content and intracellular magnesium concentration, n=25, $p<0.01$.

4. Discussion and Conclusion

There was not significant change in body weight gain of rats fed by high fat diet as

compared with the rats fed by normal fat-diet during 6 months. Importantly, the normal-fat diet was eaten 30.0 ± 5.0 g per day of a total caloric content of 3.91 cal/g; whereas the high-fat was just eaten 20.0 ± 6.0 g per day of a diet containing 5.35 cal/g. Based on exposed, we suggest that the lack of difference in the body weight gain might be due, at least in part, to the fact that the caloric ingestion was almost the same, independent of the quantity ingested. Thus, we suppose that this fact might contribute to keep body weight gain during the treatment as well as the final weight body of the rats without significant variation.

In this work, high-fat diet has promoted lipid peroxidation rat liver tissue of HF group as compared with normal fat group, demonstrated by the significantly increase in hepatic TBA-RS levels (Figure 2) and, these data are in accordance to previous papers (Folmer et al., 2003; Fachinetto et al., 2005; Greenwood & Winocur, 2005; Saiki et al., 2007). Increased TBA-RS levels found in rat livers fed by high-fat diet could be produced by two ROS pathway, which H_2O_2 and nitric oxide (NO) establish a key role in this process. Indeed, high concentrations of fats in the diet of mammals result in increased synthesis of the enzymes of peroxisomal β oxidation in the liver, generating H_2O_2 (Hashimoto, 1996), which in turn, could reacts with $O2^{\cdot-}$ producing $OH^{\cdot}$ (Halliwell, 1992; Halliwell & Gutteridge, 1986), a ROS of great toxicity in biologic systems (Halliwell, 1992; Halliwell & Gutteridge, 1986; Sastre, Pallardó & Viña, 2003). Additionally, feeding rats with high-fat contents increases the hepatic activity of inducible nitric oxide synthase (iNOS) with an enhancement of NO production, a precursor of peroxynitrite ($ONOO^-$), a potent ROS that could attack a great number of tissues producing lipid peroxidation (Pryor & Squadrito, 1995; Wan, Ohnomi & Kato, 2000). Conversely, the high fat-diet has not promoted oxidative stress in the kidney of rats (data not shown). The difference of TBA-RS production between liver and renal rats promoted by high fat-diet could be explained by differential induction of peroxisomal fatty-acid-oxidizing enzymes of these tissues. Indeed, the kidney is more refractory to induction of the peroxisomal fatty-acid-oxidizing enzymes than the liver (Sharma et al., 1989).

The route of administration of HAL decanoate (i.m.) as well as the dose of HAL used in this study was equivalent to that indicated for humans, which increase the relevance of this work since our model could be translated into the human situation. Long-term use of HAL is associated to side effects such as Parkinsonism and tardive dyskinesia, and these syndromes have been attributed to a toxic metabolite of HAL, the pyridinium metabolite HPP+ (Wright et al., 1998). Nevertheless, there are few reports demonstrating the toxic effects of HAL on the liver (Telles-Correia et al., 2017) or kidney. Since haloperidol is widely used in clinical practice, the knowledge of its toxicity is essential in the choice of this antipsychotic agent.

The results presented here showed that HAL alone only altered hepatic TBA-RS levels of the animals treated with a high fat diet, without affect the TBA-RS levels in the group that received normal fat diet. Additionally, HAL did not alter the renal TBA-RS levels neither in normal nor in high fat diet treated animals. Considering that HAL is extensively metabolized in the liver with only approximately 1% of the administered dose excreted in the urine (Forsman et al., 1977), we were not surprised that this treatment did not cause any deleterious effects on kidney from treated animals. Moreover, our data are in accordance to previous data from our lab (Dalla Corte et al., 2008). However, we emphasize that our results show for the first time an increase in oxidative damage evoked by HAL plus HF diet in hepatic tissue.

We suppose that the mechanism by which HF and HAL association induced oxidative damage may be also related to CYP activity. Accordingly, the inducible effects of high fat diet on CYP enzymes could increase the production of toxic HAL metabolites, such as HPP+, thus contributing for the deleterious effects seen in the high fat diet plus HAL treatment in the liver. Therefore, the adverse effects of high fat diet plus HAL treatment observed in the liver and the absence of these effects in kidney could be explaining, at least in part by this mechanism. Accordingly, CYP enzymes are found at highest levels in the liver, and expressed at lower levels in kidney (Ronis et al., 2004; Gonzalez, 2005; Su et al., 2005). Thus, liver is expected to be the major target in which the production of toxic HAL metabolites could be elevated.

Despite long term administration of antipsychotic drugs have been involved with body weight gain in several animal models (Cope et al., 2005; Lin et al., 2006; Mondelli et al., 2013), in the present study, the weight gain was impaired significantly with HAL treatment on both treated groups (normal and high fat diet). This effect of antipsychotic drugs on body weight gain seems to be sex dependent because while female rats is prone to gain weight during the treatment, while males did not (Cope et al., 2005), which supports our findings. Additionally, our data are in accordance to previous data from our group (Fachinetto et al., 2005).

In addition, there was a statistically significant negative correlation between the intracellular Mg2+ content and abdominal fat index (Figure 4). There is not clearly understood this negative correlation between intracellular Mg2+ and abdominal fat, however in the pathogenesis of morbid conditions an ionic hypothesis could be considered relevant. Indeed, in the onset of pathologies as DM and hypertension there may be an altered ionic metabolism, which causes a reduction in the intracellular Mg2+ (Rayssiguier et al., 1993; Paolisso & Barbagallo, 1997; Vormann, 2003). Abdominal fat may decrease intracellular

Mg2+ and recent data indicate that hypomagnesemia may be linked to the development of diabetic complications via reduction in the rate of inositol transport and subsequent intracellular depletion (Freedman et al., 1999). Additionally, the ionic aspects investigated in insulin resistance, over all in DM and metabolic syndrome suggest that depletion of intracellular free Mg2+, usual in both conditions may help in the hypothesis that the intracellular Mg2+ contents plays a role on general cellular metabolism, especially on cellular glucose homeostasis and insulin sensibility in muscle and adipose tissues (Rayssiguier et al., 1993; Paolisso & Barbagallo, 1997; Moram & Romero, 2003; Vormann, 2003).

Besides, glutathione (GSH) is the most abundant intracellular thiol in living aerobic cells. It has been assigned several critical functions as protection of cells against oxidative damage and detoxification of foreign compounds (Salgueiro et al., 2016). Accordingly, low GSH levels have been associated with the pathology of a number of diseases like AIDS, DM, and neurological disorders (Folmer, Soares & Rocha, 2002; Fachinetto et al., 2005; Ige, Adewoye & Makinde, 2016). The synthesis of GSH is Mg2+ dependent (Ige, Adewoye & Makinde, 2016) and the depletion of this ion is linked to decreased GSH levels and increased intracellular H_2O_2. Thus, in spite of no significant decrease in intracellular Mg2+ levels on our treatment design (data not shown), we could speculate that a proportional decrease in Mg2+ levels as compared to abdominal fat could be, at least in part, responsible for a decrease in GSH content, thus contributing to the deleterious effect of the HAL toxic metabolite (HPP+) on hepatic tissue.

In conclusion, the results of this study support the hypothesis that consumption of HF diet can lead to the development of lipid peroxidation in liver of rats, and that HAL treatment potentiates the hepatic oxidative damage induced by a high fat diet. However, neither diet nor HAL treatment causes renal oxidative damage in the animals. Thus, the findings from our study suggest an adverse effect from the interactions between high fat diet and HAL, which could be able to cause hepatic damage related to oxidative stress. However, further works are needed to confirm the exact mechanism by which these compounds cause oxidative stress. Finally, the negative correlation between the intracellular Mg2+ levels and the abdominal fat accumulation suggest a possible involvement of Mg2+ in the metabolic syndrome development associated with a HF diet. However, more investigations should be made to assess the possible mechanisms.

There are two major limitations in this study that could be addressed in future researches. Firstly, the research findings were limited by the exclusive use of male rats, since clinical evidence indicates greater alterations in females. The results of the present study are

also limited because the proposed mechanisms require further study. Thus, the nature of our experimental design makes difficult large generalizations.

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