41 - EFFECT OF THE BLOCKADE OF THE AT1 RECEPTOR OF ANGIOTENSIN II ON SPERMATOGENESIS AND MORPHOLOGY OF SPERMATOZOA OF OBESE WISTAR RATS

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doi: 10.16887/85.a2.41

INTRODUCTION

Obesity is a major public health problem (Kloet et al. 2014) and according to the World Health Organization (WHO 2000) there are 1.5 billion overweight adults in the world and about 12% of world population is considered obese.

Changes in metabolism observed in obesity have strong influences on reproductive functions (Dupont et al. 2013). The obesity in men is associated with a decreased concentration of spermatozoa (Shayeb et al. 2011), alteration of pH of seminal fluid, the rate of increase and decrease in atypical sperm motility and vitality of spermatozoa (Bonde 2009), erectile dysfunction and infertility (Shiri et al. 2004). Furthermore, reduced motility and increased DNA fragmentation in the sperm (Rybar et al. 2011) are observed. Studies have shown that body fat, when excessive, can cause oxidative stress, which increases the concentration of free radicals in the bloodstream and causes damage of the sperm DNA (Bakos et al. 2011). The increase of free radicals causes highly reactive oxygen, lowering the quality of germ cells in mice (Fernandes et al. 2011) and men (Vigueras-Villaseñor et al. 2011).

The renin-angiotensin system (RAS) besides its well known role as a regulator of extracellular fluid volume and blood pressure (De Gasparo et al., 2000), appears to be an important mediator of physiological and pathological effects in obesity (Zorad et al., 2006) and in the reproductive process (Herr et al. 2013). Activation of the RAS has an important role in the pathogenesis of erectile dysfunction in diabetes (Fraga - Silva et al 2013) and Ang II increased contribute to sexual dysfunction and spermatogenic in hypertensive rats (Weissheimer 2012). Administration of losartan, an antagonist of the angiotensin II AT1 receptor improves testicular inflammation (Welter et al. 2014) and coital function in men (Baumhakel et al. 2008. Considering all this evidence, the present study aimed to verify whether the use of blocking AT1 Ang II receptor antagonists may be beneficial in order to reduce possible changes in spermatogenesis and / or sperm morphology in obese rats.

METHODS

Animals

Wistar rats (n = 18) from the Universidade Estadual do Oeste do Paraná (UNIOESTE), Brazil, were kept in polypropylene cages (41 cm long X 34 cm wide X 17 cm high), in groups of three rats per cage, with light-dark cycle of 12 hours and controlled temperature (22 ± 1). All procedures of this studyt were approved by the University Committee of Ethics on Animal Care.

Groups and treatments

From 21 days up to the date of euthanasia (90 days old), animals were fed with daily standard chow diet (Algomix, Toledo, PR, Brazil) and water (CTL group) or with the cafeteria diet that included foods such as breads, candies, meats, crackers and soda without gas (Goularte et al. 2012). The animals had free access to diets. From 70-day-old, animals of the control group received water by gavage and the cafeteria group was divided into 02 groups: half received water by gavage (CAF group), and the other half received 30 mg / kg body weight / day of Losartan (Landgraf et al 2011; CAF + LOS group). A total of 6 animals were used in each group.

Assessment of obesity

After euthanasia by decapitation, the perigonadal and retroperitoneal fat were isolated and weighed. For the assessment of obesity in animals, we calculated the relative weight of fat [fat weight (g) / body weight (g)].

Histological analysis and evaluation of the spermatogenic process (dynamics of spermatogenesis)

The histological slides of the testes of animals, stained with HE were evaluated in blind, with the aid of a light microscope, the increases of 100, 200 and 400X. The tubules were classified according to Leblond and Clermont (1952).

Maturity of the epithelium of the seminiferous tubules and sperm morphology assessment

The analysis of the degree of maturity was performed according Lamano Carvalho et al. 1996. On the assessment of morphology, to collect sperm, the left vas deferens of the animals was collected and washed internally with 1.0 mL of saline and formalin-content was stored in a plastic tube. Smears were made on slides with the material collected and then with the aid of a microscope at magnification of 400 x 100 sperm were examined per animal. The morphological abnormalities found in sperm abnormalities were classified into the head (without or without curvature feature curvature - head straight and head isolated) and abnormalities of the tail (curled or broken).

Statistical analysis

One-way ANOVA, with test "a posteriori" Tukey-Kramer - For data analysis, the statistical test for analysis of variance was used. Differences were considered statistically significant when $p < 0.05$. Statistical analyzes were performed in Instat (version 3.0; GraphPad, Inc., San Diego, CA, USA) program.

RESULTS AND DISCUSSION

In the present study we investigated the relationship among diet-induced obesity and cafeteria use of angiotensin II AT1 receptor blocker losartan with spermatogenic dynamics in male rats.

The determination of absolute and relative weights of organs such as the testes, epididymis and seminal gland are useful parameters in assessing risk on the male reproductive system. By analyzing the results we observed that the cafeteria diet did not alter the weight of reproductive organs in study groups (Table 1), corroborating other studies (Fernandez et al. 2011) and

contradicting other studies that showed a decrease in the weight of testis, epididymis (Vendramini et al. 2013) and the seminal gland (Fernandez et al. 2011) in obese rats. Furthermore, the cafeteria diet did not increase the body weight of mice, in contradiction with the significant increase in body weight in the group fed a hypercaloric diet verified in other studies (Hosseini et al. 2014). These studies also showed that the increase in body weight in animals in groups fed with cafeteria diet is reduced by the administration of losartan (Smith et al. 2014). Moreover, in this study, the use of losartan did not affect the body weight of mice, similar to results observed by our recent research group (Sagae et al. 2013).

Table 1: Body and reproductive (absolute and relative) weights of animals at 90th days.

	CTL	CAF	CAF+LOS
Body weight (g)	350,20 ± 27,74	356,80 ± 25,41	369,00 ± 40,07
Testis (g)	1,51 ± 0,04	1,57 ± 0,06	1,50 ± 0,07
Testis (g / 100g)	0,42 ± 0,019	0,42 ± 0,009	0,40 ± 0,013
Epididymis (g)	0,59 ± 0,02	0,60 ± 0,03	0,59 ± 0,02
Epididymis (g / 100g)	0,16 ± 0,009	0,16 ± 0,007	0,15 ± 0,007
Seminal gland (g)	1,21 ± 0,08	1,16 ± 0,03	1,13 ± 0,04
Seminal gland (g / 100g)	0,34 ± 0,03	0,29 ± 0,02	0,28 ± 0,02

Data are presented as mean ± SEM. N = 6 animals per group.

Although not alter body weight, the relative weight of retroperitoneal (Figure 1A) and perigonadal (Figure 1B) fats were higher in the cafeteria group, confirming the induction of obesity of animals and signaling a lean mass content in the cafeteria group compared the control group, in view of the lack of difference in body weight. This result is similar to those reported by Fernandez et al. 2011.

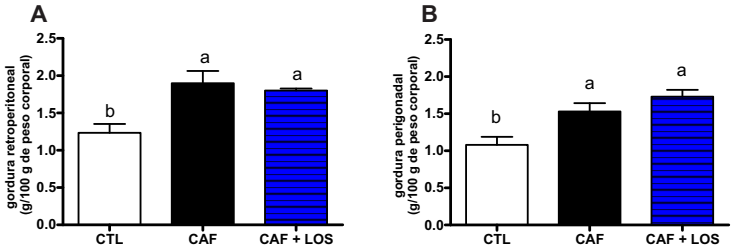

Figure 1: Effect of cafeteria diet isolated or associated with administration of losartan in absolute and relative weights of retroperitoneal fat (A) and perigonadal fat (B) of rats at 90 days of age. Same letters above bars represent statistical similarities and different letters represent statistical differences among the groups. Data are presented as mean ± SEM; P <0.05. N = 6 animals per group.

Moreover, no effect of AT1 receptor blockade on weight of fats in cafeteria group was observed in our results. This lack of effect contradicts the literature showing that the reduction or loss of function of any component of the renin-angiotensin system (RAS) leads to protection from diet-induced obesity (Tomono et al. 2008). Additionally, losartan when administered concomitantly with cafeteria diet from weaning to adulthood, prevents the accumulation of fat diet-induced (Sagae et al. 2013) and in adulthood when administered after the onset of obesity, is able to reverse the effect of diet, reducing fat accumulation to values similar to control animals (Smith et al. 2014, Gobo 2014). The lack of effect of losartan could be due to the reduced time of losartan administration in our study (20 days).

Body fat is very important to the reproductive function since adipose tissue is necessary to the production of sex hormones (Solorzano & Mccartney 2010). On the other hand, the excess adiposity is associated with reduced fertility (Dupont et al. 2013). In the present study, analysis of the cycles of the seminiferous epithelium showed no difference among the groups, which contradicts the study of Vendramini et al. 2013, which showed changes in stages of the seminiferous cycle in obese Zucker rats. Additionally, any difference in the degree of maturation of germ cells was observed between the control groups and cafeteria.

The etiology is multifactorial, and the rationale for impaired spermatogenesis in obesity pathogenic processes are still unclear. Despite the lack of differences in parameters cycle of the seminiferous epithelium and degree of maturation of the animals fed with cafeteria diet showed a significant increase in the number of abnormal sperm compared with the control group (Table 3), suggesting that the diet hypercaloric caused deleterious effects on sperm morphology and although these results should be interpreted with an awareness of interspecies differences, reinforcing the data observed in men, showing relationship between increased BMI and abnormal sperm morphology (Stokes et al. 2014), although this ratio not be considered the only criterion for the assessment of obesity (Melo & Giugliano 2004). For a better assessment of body composition is necessary to measure the nutritional status of individuals to be performed, measurements of weight, height, waist circumference (WC) and hip were observed to check the waist / hip ratio (WHR), a measure of fat tetrapolar body by bioimpedance method, among others (Rao et al. 2006).

Immunohistochemical studies confirm the presence of AT1 receptors in spermatogenic cells and has been widely reported in literaruta that angiotensin II may increase both the percentage of motile sperm and the speed thereof, accordingly, AT1 receptor antagonists, such as losartan, acting on action inhibition of Ang II on sperm cells (Vinson et al 1995).

Table 3: Morphology of sperm from animals of the different experimental groups.

	CTL	CAF	CAF+LOS
Normais (%)	77,4 ± 2,78 [b]	63,66 ± 3,42 [a]	64,5 ± 2,40 [a]
Anormalidade de cabeça (%)	12,83 ± 2,47[b]	22,83 ± 2,77[a]	20,00 ± 3,17[a]
Anormalidade de cauda (%)	9,11 ± 1,30 [b]	15,4 ± 1,80 [a]	14,5 ± 1,38 [a]

Data are presented as mean ± SEM. Same letters represent statistical similarities and different letters represent statistical differences among the groups; P <0.05. N = 6 animals per group.

Recently, we evoked a question about the administration of an AT1 blocker as beneficial for sperm cells. In this sense, as well as a certain amount of body fat is necessary for the effectiveness of male fertility and that their excess presents deleterious effects on this parameter, physiological concentrations of Ang II are important for both male as female reproduction (Sagae et al. 2012, Welter et al. 2014), however, in obesity, increased RAS activity and plasma concentrations of Ang II appear to exert adverse reproductive effects, at least in females (Sagae et al. 2013). However, the lack of effect of losartan on all parameters evaluated reproductive and especially in reversing the deleterious effect of cafeteria diet on the morphology of the sperm, could indicate, as mentioned, the need to prolong the administration of losartan, or is evident that angiotensin II through the AT1 receptor does not contribute to the reducing effect of obesity on sperm quality. Therefore, in this study the cafeteria diet induced obesity and altered the morphology of the sperm of obese rats, but the use of losartan did not reverse obesity and abnormal sperm morphology in these animals.

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EFFECT OF THE BLOCKADE OF THE AT1 RECEPTOR OF ANGIOTENSIN II ON SPERMATOGENESIS AND MORPHOLOGY OF SPERMATOZOA OF OBESE WISTAR RATS

ABSTRACT

Obesity is a chronic metabolic condition associated with numerous morbidities including cardiovascular disease, insulin resistance, hypertension and infertility. Obesity is directly associated with increased activity of renin angiotensin system (RAS). The peptide Angiontensin II is well known for his involvement in the control of body fluid and cardiovascular homeostasis and also has impact on the control of reproduction. Losartan is an antagonist of the Ang II AT1 receptor and its administration can be beneficial in order to reduce infertility resulting from obesity. The aim of this study was to evaluate the effect of blocking the AT1 Ang II receptor antagonists on spermatogenesis and sperm morphology in obese Wistar rats. After weaning male rats were treated with standard diet (CTL) or with cafeteria diet (CAF). At 70 days old, the cafeteria group was divided into two subgroups, half receiving water by daily gavage (CAF) and the other half receiving losartan by gavage, 30 mg/kg of body weight / day (CAF + LOS); the control group received water by daily gavage. The spermatogenic processes and morphology, as well as the weights of the reproductive organs and of retroperitoneal and perigonadal fats were analyzed. The cafeteria diet induced obesity by increasing the absolute and relative weight of the fats and altered the morphology of the head and tail of the sperm of the rats. Losartan did not reverse the changes caused by excess body fat in the morphology of spermatozoa. Other parameters were not altered by the cafeteria diet alone or combined with losartan. The lack of effect of losartan on all evaluated reproductive parameters may signal that he has no mediating effect thereof.

KEY WORDS: obesity, losartan, sperm processes.

POUR EFFET DE BLOQUER LE RÉCEPTEUR AT1 DE L'ANGIOTENSINE II SUR LA SPERMATOGENÈSE ET LA MORPHOLOGIE DE SPERME DES WISTAR OBÉSE RATS

RÉSUMÉ

L'obésité est une maladie métabolique chronique associée à de nombreuses pathologies notamment les maladies cardiovasculaires, la résistance à l'insuline, l'hypertension et l'infertilité. L'obésité est directement associée à une activité accrue du système rénine-angiotensine (RAS). Le peptide Angiontensin II est bien connu pour son implication dans le contrôle de fluide corporel et l'homéostasie cardiovasculaire et a également un impact sur le contrôle de la reproduction. Losartan est un antagoniste du récepteur de l'angiotensine II AT1 et son administration peut être bénéfique pour réduire l'infertilité résultant de l'obésité. Le but de cette étude était d'évaluer l'effet de blocage des antagonistes des récepteurs AT1 Ang II sur la spermatogenèse et la morphologie des spermatozoïdes chez des rats Wistar obèses. Après le sevrage chez les rats mâles ont été traités avec un régime standard (CTL) ou avec cafétéria alimentation (CAF). À l'âge de 70 jours, le groupe de la cafétéria a été divisé en deux sous-groupes, la moitié recevant de l'eau quotidiennement, par gavage (CAF) et l'autre moitié recevant losartan par gavage, 30 mg / kg de poids corporel / jour (CAF + LOS); le groupe témoin a reçu de l'eau tous les jours par gavage. Les processus de la spermatogenèse et la morphologie, ainsi que les poids des organes reproducteurs et de graisses rétropéritonéale et perigonadal ont été analysés. Le régime de la cafétéria obésité induite par l'augmentation du poids absolu et relatif des graisses et modifié la morphologie de la tête et la queue des spermatozoïdes des rats. Losartan n'a pas inverser les changements causés par la graisse corporelle en excès dans la morphologie des spermatozoïdes. D'autres paramètres ont été modifiés par pas le régime de cafétéria seuls ou en combinaison avec le losartan. L'absence d'effet du losartan sur tous les paramètres de la reproduction évalués peut signaler qu'il n'a pas d'effet de médiation de celui-ci.

EFECTO DE BLOQUEO DEL RECEPTOR DE LA ANGIOTENSINA II AT1 SOBRE LA ESPERMATOGÉNESIS Y LA MORFOLOGÍA DE RATAS ESPERMATOZOIDES WISTAR OBESO

RESUMEN

La obesidad es una condición metabólica crónica asociada con numerosas comorbilidades, incluyendo enfermedad cardiovascular, resistencia a la insulina, la hipertensión y la infertilidad. La obesidad se asocia directamente con aumento de la actividad de sistema renina-angiotensina (RAS). El péptido Angiontensin II es bien conocido por su participación en el control de fluido corporal y la homeostasis cardiovascular y también tiene impacto en el control de la reproducción. Losartan es un antagonista del receptor de Ang II AT1 y su administración puede ser beneficioso para reducir la infertilidad resultante de la obesidad. El objetivo de este estudio fue evaluar el efecto de bloquear los antagonistas del receptor AT1 de Ang II sobre la espermatogénesis y morfología de los espermatozoides en ratas Wistar obesos. Después del destete ratas macho fueron tratadas con dieta estándar (CTL) o con dieta de cafetería de Fomento (CAF). A los 70 días de edad, el grupo de la cafetería se dividió en dos subgrupos, la mitad de recibir agua por sonda diariamente de Fomento (CAF) y la otra mitad recibir losartán por sonda, 30 mg / kg de peso corporal / día (CAF + LOS); el grupo de control recibió agua por sonda diariamente. Se analizaron los procesos y la morfología de espermatogénesis, así como los pesos de los órganos reproductivos y de grasas retroperitoneales y perigonadal. La dieta de cafetería obesidad inducida por el aumento del peso absoluto y relativo de las grasas y alteró la morfología de la cabeza y la cola de los espermatozoides de las ratas. Losartán no revertir los cambios causados por el exceso de grasa corporal en la morfología de los espermatozoides. Otros parámetros no se alteraron por la dieta de cafetería solos o combinados con losartán. La falta de efecto de losartán en todos los parámetros evaluados reproductivos puede indicar que no tiene ningún efecto mediador de la misma.

EFEITO DO BLOQUEIO DO RECEPTOR AT1 DE ANGIOTENSINA II SOBRE A ESPERMATOGÊNESE E A MORFOLOGIA DE ESPERMATOZOIDES DE RATOS WISTAR OBESOS

RESUMO

A obesidade é uma condição metabólica crônica associada a inúmeras morbidades, incluindo doenças cardiovasculares, resistência à insulina, hipertensão e infertilidade. A obesidade está diretamente relacionada com o aumento na atividade do sistema renina angiotensina (SRA). O peptídeo angiotensina II é mais conhecido por seu envolvimento no controle do fluido corporal e homeostase cardiovascular, mas exerce também impacto sobre o controle da reprodução. O losartan é um antagonista do receptor AT1 de Ang II e sua administração pode ser benéfica na tentativa de reduzir a infertilidade decorrente da obesidade. O objetivo do presente estudo foi avaliar o efeito do bloqueio do receptor AT1 de Ang II sobre a espermatogênese e a morfologia de espermatozoides de ratos wistar obesos. Para tanto, ratos machos, após o desmame, foram tratados com dieta padrão (CTL) ou com dieta da cafeteria (CAF). Aos 70 dias de vida o grupo CTL recebeu gavagens diárias de água; o grupo cafeteria foi dividido em dois subgrupos, sendo que a metade recebeu gavagens diárias de água (CAF) e a outra metade recebeu gavagens diárias de losartan, 30mg/Kg de peso corporal/dia (CAF+LOS). Foram avaliados o peso corporal, os pesos dos órgãos reprodutivos, das gorduras retroperitoneal e perigonadal bem como os processos espermatogenicos e a morfologia espermática. A dieta de cafeteria induziu a obesidade aumentando o peso absoluto e relativo das gorduras avaliadas e alterou a morfologia dos espermatozoides. O losartan não reverteu às alterações causadas pelo excesso de gordura corporal na morfologia dos espermatozoides. Os demais parâmetros avaliados não foram alterados pela dieta de cafeteria isolada ou associada ao losartan. A ausência de efeito do losartan sobre todos os parâmetros reprodutivos avaliados pode sinalizar que ele não tem efeito mediador dos mesmos.

PALAVRAS-CHAVE: obesidade, losartan, processos espermáticos.