Adiponectin and Resistin Adipokines: Implication in Testosterone Hormone Secretion in Obese Male Rats

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Abstract

Background: Obesity in men, particularly when central, is associated with lower total testosterone [TT], free testosterone [FT] and sex hormone-binding globulin [SHBG], and a greater decline in TT and FT with increasing age compared with lean men. Obesity-related conditions such as obstructive sleep apnea, insulin resistance and type 2 diabetes mellitus are independently associated with decreased plasma testosterone. Obese men have reduced sperm concentration and total sperm count compared to lean men but sperm motility and morphology appear unaffected. The cause and effect relationships between low plasma androgen levels, obesity and the metabolic syndrome remain unclear. Adiponectin has a role in the control of the reproductive axis, which might operate as endocrine integrator linking metabolism and gonadal function. Expression, regulation and functional role of adiponectin and resistin adipokines in rat testis were documented. Both adipokines may operate as novel endocrine integrators linking energy homeostasis and reproduction.

Objective: The aim of the present study was to find out an effect of obesity on testicular mRNA gene expression of adiponectin and/or resistin adipokines. Also, to investigate a potential correlation between the mRNA expression of adiponectin and/or resistin and testicular function as indicated by serum testosterone level in obese male rats.

Material and Methods: The study was conducted on 20 male albino rats. The experimental animals were divided into 2 groups, 10 rats each. Group I: Control rats and Group II: Obese rats. After 12 weeks, all overnight-fasting rats were sacrificed. Blood samples were collected, and the testes were rapidly excised, weighed and frozen at –80ºc for further mRNA detection. The following parameters were measured: Serum fasting glucose, fasting insulin, fasting triglycerides, fasting cholesterol, insulin resistance was estimated using homeostatic model assessment (HOMA) index, serum testosterone, testicular resistin mRNA expression and testicular adiponectin mRNA expression.

Results: The results of the present work showed that serum glucose, triglycerides, total cholesterol, and insulin resistance were significantly higher in obese rats compared to the controls. Serum testosterone level and testicular adiponectin mRNA were significantly lower in obese rats, while testicular resistin mRNA was significantly higher in obese rats compared to the control. No correlations were found between testicular resistin, adiponectin, and serum testosterone in the two studied groups.

Conclusion: The present study provided a characterization of the pattern of gene expression of both adipokines: Resistin and adiponectin in the testis and showed their association with gonadal function on the basis of the level of serum testosterone. This inter-relation could suggest the biological effects of these adipokines in the male gonad.

Key Words: Obesity – Resistin – Adiponectin – Testosterone.

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Introduction

THE global epidemic of obesity in both adults and children has also been associated with the global burden of an increased incidence of chronic illness, including physical disability, cardiovascular disease, hypercholesterolemia, hypertension, stroke, type 2 diabetes and other metabolic disorders, and cancer [1]. Further, an association between infertility and obesity has been demonstrated; however, most of these studies have primarily focused on the relationship between elevated BMI, or percent body fat, in females and reduced fertility [2-4]. In contrast, the impact of obesity on male fertility has only recently begun to be explored, and in vivo studies using obese mice have produced varied results [5,6]. Studies have reported that men with higher BMIs (>25) have quantitatively and qualitatively inferior sperm, decreased serum testosterone, and increased levels of estrogen and follicle-stimulating hormone than men with BMIs ranging between 20 and 25 [1].

The integrated control of energy status and reproductive function systems is probably a multifaceted phenomenon conducted by an array of signals acting at different levels of the neuroendocrine axes, governing food intake, energy homeostasis, metabolism and fertility. For example, the
Adipocyte-derived hormone, leptin, operates as a pleiotropic regulator of several metabolic and neuroendocrine systems, including the reproductive axis, acting mainly at central hypothalamic levels [7].

In addition to the important role of sex hormones in reproduction, there is evidence that they also influence glucose metabolism. Clinical and epidemiological findings have related androgen levels with insulin resistance (IR). Several studies have reported that serum testosterone concentration in men correlates inversely with insulin concentration [8,9]. It has also been found that low testosterone concentrations increase the risk of type 2 diabetes [10-12], and that the administration of androgens in hypogonadal men appears to improve insulin sensitivity [13].

In addition to sex hormones, certain adipocytokines such as leptin, adiponectin, and resistin had been associated with the appearance of IR and the maintenance of metabolic homeostasis [14]. Resistin, an adipocytokine belonging to the family of small cystine-rich proteins, is produced mainly by adipocytes in mice [15] and by macrophages and monocytes in humans [16]. Initially, resistin was reported to antagonize the action of insulin in rodents, and resistin levels were found to be increased in diabetic and obese mice [15]. These early findings suggested that resistin might be a link between obesity and IR. However, later studies in rats and humans have yielded contradictory findings [17-20] and the role of resistin in the appearance of IR remains controversial.

Resistin gene expression was demonstrated in rat testis throughout postnatal development, with maximum mRNA levels in adult specimens. At this age, resistin peptide was immunodetected in interstitial Leydig cells and Sertoli cells within seminiferous tubules. Testicular expression of resistin was under hormonal regulation of pituitary gonadotropins and showed stage-specificity, with peak expression values at stages II-VI of the seminiferous epithelial cycle. From a functional standpoint, resistin, in a dose-dependent manner, significantly increased both basal and choriogonadotropin – stimulated testosterone secretion in vitro. These data underscore a reproductive facet of this recently cloned molecule, which may operate as a novel endocrine integrator linking energy homeostasis and reproduction [21]. Furthermore, resistin has also been reported to be involved in the control of adipocyte differentiation [22].

It is well known that reproductive capacity is metabolically gated, and an ever growing number of neuropeptides and hormone signals, primarily involved in the control of energy balance and metabolism, have been recently proven as putative regulators of puberty maturation, gonadotropin function, and/or fertility [23]. Among those, the prominent role of the adipocyte-derived hormone, leptin, in the control of reproduction has been well characterized over the last decade [24,25]. In contrast, the physiological role, if any, of other adipose-borne signals in the modulation of reproductive function remains ill defined. Notwithstanding, given its functional profile, the putative reproductive functions of adiponectin have begun to be explored recently. These analyses were initially focused in the eventual implication of adiponectin in female reproductive disorders linked to obesity and insulin resistance, such as polycystic ovarian syndrome. Indeed, a decrease in circulating adiponectin levels has been reported in polycystic ovarian syndrome patients [26,27]. Further evidence for a physiological link between adiponectin and reproductive function came from the observation that adiponectin concentrations are invariably higher in females than in males [28] and that androgens inhibit adiponectin secretion [29,30].

In the light of the above considerations, the aim of the present study was to find out an effect of obesity on testicular mRNA gene expression of adiponectin and/or resistin adipokines. Also, to investigate a potential correlation between the mRNA expression of adiponectin and/or resistin and testicular function as indicated by serum testosterone level in obese male rats.

Material and Methods

Experimental animals:

Twenty male albino rats with mean body weight 150-180gm obtained from the animal house of faculty of medicine, Cairo University were included in the present study. The rats were housed in wire mesh cages singly, maintained at optimum environmental temperature with 12:12 dark-light cycles. Veterinary care was provided by laboratory Animal House Unit of Cairo University.

Animal groups:

The animals were randomized into two groups. Each group comprised ten animals.

Group I: Control rats (n=10)

They had free access to laboratory rat chow and tap water throughout the study for 12 weeks. The laboratory rat chow consisted of the following ingredients (Carbohydrates: Corn starch 480g/Kg diet & Sucrose 100g/Kg diet, Fats: Soybean oil
Group II: Obese rats (n=10)

They had free access to high fat diet and tap water throughout the study period for 12 weeks. The high fat diet was weekly prepared and stored. The food was renewed every day for the 12-week diet course. The experimental high fat diet consisted of the following ingredients (Carbohydrates: Corn starch 100g/Kg diet & Sucrose 100g/Kg diet, Fats: Soybean oil 50g/Kg diet & Lard 500g/Kg diet, Protein: Casein 190g/Kg diet).

All rats were weighed in grams and naso-anal lengths were measured in mm at the beginning and at the end of the 12-week study. The body mass index (BMI) was calculated by dividing the body weight in kilograms by the length in meters squared.

After 12 weeks, blood samples from all overnight-fasting rats were collected by introducing fine heparinized capillary tube at the inner canthus of the eye into the venous plexus. Then, all rats were sacrificed and the testes were rapidly excised, weighed and frozen at –80°C for further mRNA detection.

Biochemical measurements:
1- Serum fasting glucose, fasting insulin, triglycerides, total cholesterol, using commercially available kit.
2- Insulin sensitivity was estimated using homeostatic model assessment (HOMA) index (i.e. plasma glucose x insulin/22.5) insulin resistance (IR) was defined as HOMA ≥54.
3- Serum testosterone level: Serum testosterone levels were assayed in duplicate from trunk blood using a double antibody kit (Diagnostic Systems Labs, Webster, TX, USA) with a minimum detection limit of 0.05ng/ml and a range up to 25ng/ml.

Detection of adiponectin and resistin gene expression by Reverse transcription -polymerase chain reaction (RT-PCR): RNA extraction:

Total RNA was extracted by acid guanidinium thiocyanate-phenol-chloroform method. RNA content and purity was measured using ultraviolet spectrophotometer (A260/A280 ratio of 1.8-2.0). For amplification of the target genes, reverse transcription-PCRs were run in two separate steps.

In brief, equal amounts of total RNA (6mg) were heat denatured and reverse transcribed by incubating at 42 1C for 90min with 12.5U (avian myeloblastosis virus) reverse transcriptase (Promega, Madison, WI, USA), 200nM deoxyribonucleotide triphosphate mixture and 1nM oligo-dT primer in a final volume of 30ml of 1×avian myeloblastosis virus buffer. The reactions were terminated by heating at 97 1C for 5min and cooled on ice.

Complementary DNA samples were amplified in 50ml of 1×PCR buffer in the presence of 2.5U Taq DNA polymerase(Promega), 200 nM deoxyribonucleotide triphosphate mixture and appropriate primer pairs (1 nM of each primer) for adiponectin forward primer 50-CTGAGCTGACCTTGGAGC-30, reverse primer 50 GACTCCAGCCAACAAAGATG-30; for resistin forward primer 50 GGAGGCACCTCCGAG-30 and reverse primer 50-GCCTGGCATCACGACT-30. PCR consisted in a first denaturing cycle at 97 1C for 5min, followed by a variable number of cycles of amplification defined by denaturation at 96 1C for 1.5 min, annealing for 1.5min and extension at 72 1 C for 3min. A final extension cycle of 72 1 C for 15 min was included. PCR products were electrophoresed on 2% agarose stained with ethidium bromide and visualized by ultraviolet transilluminator. Semiquantitation was performed using gel documentation system (BioDO, Analyser, Biometra, Göttingen, Germany). According to the amplification procedure, relative expression of each studied gene (R) was calculated following the formula: R = 1/4 densitometrical units of each studied gene/densitometrical units of b-actin.

Presence of RNA in all samples was assessed by analysis of the 'house-keeping' gene β-actin. Complementary DNA was generated from 1mg total RNA extracted with avian myeloblastosis virus reverse transcriptase for 60min at 37 1C. For PCR, 4ml complementary DNA was incubated with 30.5ml water, 4ml 25mM MgCl₂, 1 ml deoxyribonucleotide triphosphates (10mM), 5ml 10×PCR buffer, 0.5ml (2.5U) Taq polymerase and 2.5ml of each primer containing 10 pM. β-actin primers (forward 50-TGTAGTCCGATGAGCTTCTCTTCTCTTATCCGATTTCC-30; reverse 50-TAATGTCACGCACGATTTCC-30) was designed from Gen Bank (accession no. J00691). The reaction mixture was subjected to 40 cycles of PCR amplification, denaturation at 95 1C for 1min, annealing at 57 1C for 1min and extension at 72 1 C for 2min.

Statistical analysis:

The data was coded and entered using the statistical package SPSS version 15. The data was summarized using descriptive statistics: Mean,
standard deviation, minimal and maximum values for quantitative variables. Statistical differences between groups were tested using Nonparametric Mann Whitney test for quantitative variables, which aren’t normally distributed. Correlations were done to test for linear relations between variables. \( p \)-values less than or equal to 0.05 were considered statistically significant.

**Results**

The results of the present study were summarized in the following Tables (1-3) and Figs. (1-3).

**Body weight and body mass index:**

A statistical significant \( (p<0.05) \) increase in body weight was observed in male rats consuming the high-fat diet in comparison to age-matched rats eating a laboratory rat chow diet. Rats consuming the high-fat diet swelled to weights averaging 327.17\( \pm \)43.13 grams at the end of the study, whereas rats on the laboratory rat chow diet at the same age averaged 168.67\( \pm \)21.04 grams (Table 1). Body mass indices were also significantly higher in high-fat-fed rats versus laboratory rat chow-fed rats, averaging 6.48\( \pm \)0.44 and 3.22\( \pm \)0.18, respectively (Table 1). Therefore, rats fed a laboratory rat chow diet were classified as control and rats fed a high-fat diet were classified as obese throughout the study.

**Testis weight and testis weight/body weight ratio:**

A statistical significant \( (p<0.05) \) increase in testes weights were observed in obese rats compared to control rats, however, the testis weight \( (\text{mg})/\text{body weight (g)} \) ratio was significantly \( (p<0.05) \) reduced in obese rats (Table 1). The testis weight/body weight ratio was used to measure the effect of obesity on the testis size and growth.

**Effect of diet on serum glucose, insulin, cholesterol, triglycerides, and HOMA:**

Table (2) shows the mean values \( \pm \) Standard deviations (SD) of serum fasting glucose (in mg/dL), serum fasting insulin (in ng/dL), serum triglycerides (in mg/dL), serum total cholesterol (in mg/dL) and homeostatic model assessment (HOMA) index in control and obese rats. Obese male rats exhibited notably statistical significant increase \( (p<0.05) \) of serum fasting glucose, serum fasting insulin & homeostatic model assessment (HOMA) index (indicating insulin resistance) and significant \( (p<0.05) \) increase of serum triglycerides & total cholesterol (indicating hyperlipidemia) compared to control rats.

**Testicular adiponectin and resistin mRNA expression and serum testosterone level:**

Table (3) shows the mean values \( \pm \) Standard deviations (SD) of serum testosterone level (in ng/ml), testicular resistin mRNA level (in \( \mu \text{g/dL} \)) and testicular adiponectin mRNA level (in \( \mu \text{g/dL} \)) in control and obese rats.

There was statistical significant reduction \( (p<0.05) \) of serum testosterone in obese rats compared to control rats (Table 3 and Fig. 1). As regards the testicular gene expression of adipokines’ mRNA, there was statistical significant increase \( (p<0.05) \) in testicular resistin mRNA in obese rats compared to control rats (Table 3 and Figs. 2a,b), in contrast there was statistical significant reduction \( (p<0.05) \) in testicular adiponectin mRNA in obese rats than control rats (Table 3 and Figs. 3a,b).

The results of current study showed no correlation between serum testosterone level (in ng/ml) and testicular adiponectin mRNA level (in \( \mu \text{g/dL} \)) and testicular resistin mRNA level (in \( \mu \text{g/dL} \)) and no correlation between testicular resistin mRNA level (in \( \mu \text{g/dL} \)) and testicular adiponectin mRNA level (in \( \mu \text{g/dL} \)) in both control and obese rats.

Table (1): Mean Values \( \pm \) standard deviations of body weight (in gm), body mass index, testis weight (in mg), testis weight (in mg)/body weight (in gm) ratio, in control and obese groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n=10)</th>
<th>Obese group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>168.67( \pm )21.04</td>
<td>327.17( \pm )43.13*</td>
</tr>
<tr>
<td>Body mass Index</td>
<td>3.22( \pm )0.18</td>
<td>6.48( \pm )0.44*</td>
</tr>
<tr>
<td>Testis weight (mg)</td>
<td>1300( \pm )115.47</td>
<td>1553.33( \pm )220.51*</td>
</tr>
<tr>
<td>Testis weight (mg) / Body weight (g) ratio</td>
<td>7.80( \pm )1.21</td>
<td>4.76( \pm )0.60*</td>
</tr>
</tbody>
</table>

* Significant difference \( (p<0.05) \) in comparison to control group.

Table (2): Mean Values \( \pm \) standard deviations of serum fasting glucose (in mg/dL), serum fasting insulin (in mg/dL), serum triglycerides (in mg/dL), serum total cholesterol (in mg/dL) and homeostatic model assessment (HOMA) index in control and obese groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n=10)</th>
<th>Obese group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum fasting glucose (mg/dL)</td>
<td>90.61( \pm )8.95</td>
<td>156.72( \pm )19.60*</td>
</tr>
<tr>
<td>Serum fasting insulin (mg/dL)</td>
<td>10.56( \pm )1.86</td>
<td>25.23( \pm )4.084*</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>54.58( \pm )3.27</td>
<td>77.50( \pm )7.27*</td>
</tr>
<tr>
<td>Serum total cholesterol (mg/dL)</td>
<td>136.37( \pm )12.03</td>
<td>169.80( \pm )16.94*</td>
</tr>
<tr>
<td>HOMA</td>
<td>44.17( \pm )4.964</td>
<td>182.498( \pm )37.005*</td>
</tr>
</tbody>
</table>

* Significant difference \( (p<0.05) \) in comparison to control group.
Table (3): Mean Values ± standard deviations of serum testosterone level (in ng/ml), testicular resistin mRNA level (in µg/dl) and testicular adiponectin mRNA level (in µg/dL) in control and obese groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n=10)</th>
<th>Obese group (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum testosterone (ng/mL)</td>
<td>1.27±0.41</td>
<td>0.85±0.20*</td>
</tr>
<tr>
<td>Testicular resistin mRNA (µg/dl)</td>
<td>0.03±0.01</td>
<td>0.45±0.29*</td>
</tr>
<tr>
<td>Testicular adiponectin mRNA (µg/dL)</td>
<td>0.48±0.13</td>
<td>0.22±0.12*</td>
</tr>
</tbody>
</table>

* Significant difference (p<0.05) in comparison to control group.

Fig. (1): Mean values and standard deviations of serum testosterone levels (in ng/ml) in control and obese rats.

Fig. (2-A): RT-PCR mRNA expression of resistin gene in testicular tissue of control and obese rats.

Fig. (2-B): Mean values and standard deviations of resistin mRNA levels (in µg/dl) in testicular tissue of control and obese rats.

An agarose gel electrophoresis show PCR products of resistin gene expression.
Lane M: DNA marker with 100 bp.
Lane 1 : PCR product in control group.
Lane 2 : PCR product of obese group.

Fig. (3-A): RT-PCR mRNA expression of adiponectin gene in testicular tissue of control and obese rats.

Fig. (3-B): Mean values and standard deviations of adiponectin mRNA levels (in µg/dL) in testicular tissue of control and obese rats.

* Significant difference in comparison to control group.
Discussion

Although the exact pathophysiological mechanisms remain unclear, leptin, resistin, ghrelin [40] and adiponectin [41] appear to play crucial roles in the interaction between obesity and testicular function. Among the diversity of target tissues and cellular functions, expression and/or direct actions of different adipokines have been reported in the gonads [41]. In the present study, obesity of adult male rats was induced by high fat diet in a trail to find out the effect of obesity on testicular adipokines: Adiponectin and resistin mRNA expressions and to find out if testicular adiponectin and resistin mRNA expressions are correlated with testosterone secretion.

Endocrine dysregulation has been shown to be a primary characteristic of male obesity, particularly the development of insulin resistance [42]. Free fatty acids and adipokines synthesized in adipose tissue have a significant influence on glucose homeostasis. Adipokines are the main regulators of insulin sensitivity and therefore a potential link between obesity and insulin resistance [21,43,44].

In the present study, we found higher fasting blood glucose level, higher fasting blood insulin level and increased HOMA , which indicate insulin resistance, in obese rats compared to control rats. Similar results were also observed in other studies [1,42] which suggested that the hypogonadism in people with obesity is in large part attributable to insulin resistance and/or hyperinsulinemia.

Bruning et al. [45] suggested that, insulin imparts neuroendocrine regulation to mouse fertility. Mice with a neuron-specific disruption of the insulin receptor gene (NIRKO) displayed an obesity phenotype characterized by hypertriglycerideremia, hypercholesterolemia, hyperinsulinemia and elevated insulin resistance, mirroring the pathologies of the diet-induced obesity model presented in the current work. Matings between male NIRKO mice and control females produced a 30% reduction in the number of offspring in comparison to control matings. The decline in male NIRKO fertility was attributed to decreased sperm count and impaired spermatogenesis [45].

The results of the present study was in accordance with the results of Skrypnyk [46] studies which testified that insulin resistance in patients with metabolic syndrome and type 2 diabetes mellitus is associated by the decrease in the level of adiponectin and increase in the level of resistin. Lower level of adiponectin and higher level of resistin in blood serum can be examined as markers of the metabolic syndrome and the content of adiponectin in blood serum negatively correlates with an insulin resistance index HOMA.

Of note, circulating levels of adiponectin are inversely correlated with the degree of adiposity and are overtly reduced in obesity and type 2 diabetes, whereas adiponectin administration has been shown to ameliorate insulin resistance and to induce glucose lowering in animal models of obesity. As a whole, these observations strongly suggest that decreased adiponectin levels are likely to operate as causative link between excess of adiposity and related comorbidities [41].

In addition, our results were in accordance with that of Goulis, et al. [40], who found that obesity affects testicular function by reducing total testosterone and sex hormone-binding globulin levels, as well as having a detrimental effect on spermatogenesis. On the other hand, hypogonadism further increases insulin resistance, which is the main pathophysiological feature of metabolic syndrome. There are implications that testosterone replacement can improve not only testicular function, but also parameters of the metabolic syndrome. Independent mechanisms of oxidative stress through the generation of reactive oxygen species in the testes, continuous exposure to elevated serum lipids transversing the blood-testis barrier, and the accumulation of free radicals and fatty acids in the testes of obese rats presented in the current work may have collectively contributed to impaired testicular function [47].

In a longitudinal study of rhesus monkeys that had free access to food and became obese and subsequently developed type 2 diabetes, the reduction of plasma adiponectin preceded the development of hyperinsulinemia and hyperglycemia [48]. It was also demonstrated, in monkey and human, that plasma adiponectin levels correlated significantly with insulin sensitivity in the whole body using the hyperinsulinemic-euglycemic glucose clamp technique [48,49]. Recent studies demonstrated that adiponectin increased fatty acid oxidation, augmented insulin action in the muscle and liver, and further improved insulin resistance in lipoatrophic and genetically obese mice, both of which had hypoadiponectinemia [50]. These observations indicate that adiponectin is an insulin-sensitizing hormone and that hypoadiponectinemia induces insulin resistance. The relationships between androgens, resistin, and adiponectin have not been firmly established, and the relationships between serum androgen concentrations and testicular resistin and adiponectin mRNA remain to be understood.
The present study provided a characterization of the pattern of gene expression of both adipokines; resistin and adiponectin in the testis and showed their association with gonadal function on the basis of the level of serum testosterone, the testicular mass and testis weight/body weight ratio. The testis weight/body weight ratio was used to measure the effect of obesity on the testis size and growth [51]. This inter-relation could suggest the biological effects of these adipokines in the male gonad.

The expression of adiponectin in the rat testis was documented in this study by the analytic approach at the mRNA level. This finding was in accordance with the work of Caminos, et al. [41] who observed discernible adiponectin immunoreactivity in testicular sections from adult rats, with prominent signals being detected in interstitial Leydig cells. However, faint to negligible immunostaining was observed in the seminiferous tubules, regardless of the stage of the epithelial cycle. The latter observation strongly suggested that the major source of testicular expression of adiponectin is located at the interstitium, likely in steroidogenic Leydig cells, in which this adipokine might play a functional role in the local (autocrine) control of testosterone secretion.

In addition, the testicular expressions of both adiponectin receptors, AdipoR1 and AdipoR2, mRNAs were demonstrated, with a rather compartmentalized pattern of distribution. AdipoR1 mRNA was clearly expressed in the seminiferous epithelium, whereas expression of AdipoR2 mRNA was not detected in the seminiferous epithelium, but likely confined to the interstitium. The latter was under the regulation of developmental cues and gonadotropins because AdipoR2 mRNA levels increased at puberty transition and were significantly enhanced by the superagonist of LH, hCG, a phenomenon that might be causative for the observed pubertal rise of AdipoR2 mRNA in the rat testis [41].

Caminos, et al. [41] concluded that whereas testicular and adipose expression of adiponectin gene may share common regulatory signals, the effects of some of those regulators appear to be tissue specific. The relevance of such metabolic modulation of adiponectin expression in the rat testis merits further investigation.

The data presented by this work indicate that obesity is associated with low serum testosterone level, low testicular adiponectin mRNA expression and high testicular resistin mRNA expression.

Correlations between serum testosterone level, testicular adiponectin mRNA expression and testicular resistin mRNA expression could not be found in both studied groups.

Whereas the work of Nogueiras, et al. [21] showed that testicular resistin mRNA remained unaltered in a model of diet-induced obesity. While the studies of Steppan, et al. [43] and others [52] showed that plasma resistin levels were significantly elevated in genetically susceptible and diet-induced obese mice.

The role of resistin in insulin sensitivity and obesity is controversial. Some authors suggest that increased serum resistin levels are associated with obesity, visceral fat, insulin resistance, type 2 diabetes and inflammation, while others failed to observe such correlations. As Ukkola [54] had reported increased resistin expression in human abdominal tissue, other studies [53,55] however, had reported reduced resistin expression in human and rat obesity, as insulin, FFAs, and TNF-α had all been shown to inhibit resistin expression and all of these factors were elevated in obesity.

Whether the effect of resistin in the testis due to paracrine or central action, it is not known. There is often a discrepancy between circulating protein levels of resistin and m-RNA content in adipocytes. Therefore, contrasting results obtained from both human and a rodent study made the role of resistin in obesity-induced diabetes is more and more controversial [55].

Kühn-Velten, et al. [56] interpreted the changes in testicular endocrine function in obese mice as consequences of pituitary dysfunction. The hypothalamic/pituitary/gonadal (HPG) axis is central to the mammalian reproductive system. Pulsatile release of GnRH from neurons in the hypothalamus stimulates the secretion of LH and FSH from gonadotropes in the anterior pituitary. The precise function of adiponectin on the reproductive axis has yet to be uncovered. Adiponectin receptors are expressed widely, including in the hypothalamus and paraventricular nucleus, raising the possibility of auto- or paracrine regulation [57].

In conclusion, our work has demonstrated that diet-induced obesity leads to significant reduction in testis weight/body weight ratio and testosterone secretion which could influence male fertility. Furthermore, testicular mRNA gene expression of adiponectin is increased and that of resistin is decreased. Collectively, hyperinsulinemia, hyperlipidemia and dysregulation of testicular gene expression associated with the consumption of a...
high-fat diet contributed to the impaired fertility of obese male rats.

As the incidence of obesity continues to escalate as a consequence of lifestyle choices, decreased exercise, and consumption of diets rich in fat, male infertility is also increasing. So, more investigations and studies are needed to clarify the correlations between obesity, adipokines and male fertility.

References


38. ROTA-HAVAS T., KÁTAY L., RÓZSA K., PAPP L., KISS I., KOTAI E., LÓRAH A. and TÁTARI N.: Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes, 50: 1126-1133.


