folia medica

Folia Medica 64(2):288-295
DOI: 10.3897/folmed.64.e65467

Original Article

High Lipid Diet and the Expression of Proinflammatory Markers in Testis

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Received: 3 March 2021 ♦ **Accepted:** 2 June 2021 ♦ **Published:** 30 Apr 2022

Citation: Pencheva M, Koeva I, Dimitrov I, Daskalova E. High lipid diet and the expression of proinflammatory markers in testis. Folia Med (Plovdiv) 2022;64(2):288-295. doi: 10.3897/folmed.64.e65467.

Abstract

Introduction: Obesity is defined as chronic low-grade inflammation which is manifestation of the cellular response to a variety of stressful situations leading to organ and tissue damage. A high lipid diet could be assumed to be the trigger mechanism for the development of inflammatory processes leading to a disorder in the immune tolerance in the testis.

Aim: The present study aimed at demonstrating the expression of inflammatory markers in the testis by a model of a high lipid diet and the possible effect on spermatogenesis.

Materials and methods: Male Wistar rats were used in the study divided into two groups: a control group fed standard rodent food and an experimental group receiving high lipid food for 14 weeks. Routine histological techniques, immunohistochemical reactions for proinflammatory markers and morphometric analysis were performed to examine the testis preparations.

Results: The high lipid diet caused a low-grade inflammation in the testis in the experimental group, which was confirmed by the increase of proinflammatory markers: the C-reactive protein, serum amyloid A, and interleukin-4, and by the elevated levels of angiotensin-converting enzyme in the experimental versus control groups in a rat experimental model.

Conclusions: Our results suggest that a high lipid diet might be a possible cause for the idiopathic infertility in men.

Keywords

ACE, fertility, IL-4, obesity, SAA

INTRODUCTION

Spermatogenesis is a very well-balanced process controlled by multiple genes. It requires a specific microenvironment and precise regulation of the processes of proliferation and apoptosis for its conduction. Ensuring and maintaining this balance leads to the creation of unique immune tolerance in the testis.[1,2]

This tolerance is due to a specific structure which is built and functions through a complex, mutually controlled interaction of a large number of cell types represented by the testicular macrophages in the interstitium[1], the myoid cells lining the seminiferous tubules, and the Sertoli cells located in the seminiferous epithelium which builds the blood-testis barrier.[2]

The testis has a spermatogenic function in the seminiferous tubules and a steroidogenic function in the Leydig cells located in the interstitial spaces. Causes leading to a disturbance of the balance could also lead to clinical pathology

and decreased spermatogenic activity. Increasing attention has been being paid to the lifestyle as a major factor in men's good health and fertility.[3,4] The immune tolerance disturbance in the testis is very often caused by external causes, in which case we consider nutrition as a factor leading to infiltration and elevation of early pro-inflammatory markers such as C-reactive protein (CRP), serum amyloid A (SAA), interleukin-4 (IL-4), and the expression of angiotensin-converting enzyme (ACE).

Adipose tissue releases a wide range of protein signals and factors including leptin, resistin, interleukin-6, IL-1β, the tumour necrosis factor, monocyte chemoattractant protein1, and adipokines such as adiponectin, and all these mediators initiate or promote inflammation.[5] Pro-inflammatory markers, such as CRP, are synthesized and secreted from the liver as a result of elevated cytokine levels.[6] SAA proteins are produced by hepatocytes and adipocytes. Their serum concentrations correlate with the body mass index.[7,8]

IL-4, initially produced by basophil cells, is a cytokine that induces the differentiation of native helper T cells (Th0 cells) into Th2 cells.[9] It also stimulates and activates T cell of B cell proliferation.[10] IL-4 is associated with the lipid deposition in adipocytes and increases the secretion of inflammatory factors that underlie low grade inflammation of adipose tissue.[11]

Adipose tissue expresses all components of the renin-angiotensin system (RAS) and all their receptors.[12] ACE is involved in the accumulation and storage of lipids in mature adipocytes functioning as a lipogenic hormone via the Ang II and AT 2 receptor.[13,14] Obesity induces a low-level inflammatory process by expressing Ang II and inflammatory cytokines mediated by Ang II from mature adipocytes.[15,16]

Despite the numerous studies on the effect of anti-inflammatory cytokines, such as IL-4, the role of pro-inflammatory markers such as CRP, SAA, and ACE in the functions of testis or obesity is still poorly understood.

AIM

The aim of the present study was to demonstrate the expression of inflammatory markers in the testis by a model of high lipid diet and the possible effect on spermatogenesis.

MATERIALS AND METHODS

Animals

Experimental animals (n=50), eight-week-old male Wistar rats (weight 130–180 g) were obtained from the University vivarium. They were randomly divided in two groups: a control group (C) fed with standard rodent food [D12450H, Research Diets, Inc. containing proteins (19.2 g%), carbohydrates (67.3 kg%), fat (4.3 g%) and energy value of 3.85 kcal/g.] for 14 weeks; and an experimental group (E) fed with a high-fat diet [D12451 Research Diets, Inc. containing proteins (24 g%), carbohydrates (41 g%), fat (24 g%), energy value of 4.73 kcal/g.] for 14 weeks.

Blood sera were collected and immediately frozen at −18°C, the tissue samples from testis were placed in Bouin's solution for immunohistochemical workup.

Immunohistochemistry

Testes were fixed in Bouin's solution for 24 hours. Sections (5 μm thick) of the testes were deparaffinised, then subjected to antigenic detection of the epitopes with citrate buffer, making an endogenous peroxidase blockade with hydrogen peroxidase 3%; a kit (ref: No. BBK 120, Scy Tek, USA) was used to block the endogenous biotin and reagent was used to block the non-specific binding (Superblock, Scy Tek) followed by incubation for 24 hours (at 4°C) with monoclonal mouse antiCRP, SAA, IL4 (1:150, Dako, Denmark), anti-goat ACE (1:300, sc 12187, San.Cruz Biot. Inc.,USA), next incubated with secondary antibody: biotinylated anti-rabbit for 10 min at room temperature.

The reaction was visualized with 3,3 diaminobenzidine tetrachloride (DAB, ScyTek Lab. Inc., USA), and counterstaining with Mayer's hematoxylin. The preparations were observed with a light microscope at 400× magnification.

Quantitative analysis of immunohistochemical reactions

Quantitative analysis of the immunohistochemical reaction was conducted using the Olympus DP-Soft image system (version 4.1 for Windows) and Microscope-SA (Nikon, Japan) system equipped with Camedia-5050Z digital camera (Olympus, Japan). The analysis was performed on sections from testis of Wistar rats (n=25 for each group of animals, controls, and the group fed the high lipid diet). The parameters were measured on 5 sections of the animal; we determined the percentage of cells expressing CRP, SAA, IL-4, and ACE in the seminiferous tubules and the testicular interstitial cells. For each antibody was analyzed for 5 fields of the testis of each animal in each of them by means of a graduated grating (6×5 fields, each field having a size of 100 μm^2) was determined average number of cells with positive unit area response at ×400 magnification.

Statistical analysis

The data were expressed as the mean ± standard error of the mean (SEM). The number of tissue preparations used in each experiment is indicated by n. The Student t-test was used to reveal any statistically significant differences. A p-value less than 0.05 was considered statistically significant.

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RESULTS

Fifty eight-week-old male Wistar rats were used in this experiment for 14 weeks. They were randomly divided in two groups: a control group (C) (n=25) fed with standard rodent food (D12450H, Research Diets, Inc.) and an experimental group (E) (n=25) fed with a high-fat diet (D12451 Research Diets, Inc.), causing obesity.[17]

At baseline, the median weight of the experimental Wistar rats was 145 g, (95% CI 141.47–149.36). At the end of the experiment, the two groups had a pronounced difference in their weight: for group C it was 294 g, (95% CI 269.22–322.53) and for group E – 367.50 g (95% CI 340.65–379.60) (p=0.002) **(Table 1)**.

Expression of CRP, SAA, Il-4, and ACE in two groups

We used immunohistochemical stains to determine the level of expression of CRP, SAA, IL-4, and ACE markers in the testis **(Fig. 1)**.

CRP in the control and experimental groups was found to be expressed in the Leydig cells, undifferentiated spermatogonia, round and elongated spermatids, head and tail of mature spermatozoa. The analysis of the data showed increased expression in the experimental group **(Fig. 1 CRP)**.

SAA was expressed predominantly in the Leydig cells and in the undifferentiated spermatids from the experimental group; however, this was not evident in the control group **(Fig. 1 SAA).**

Semi-quantitative analysis for IL-4 showed higher expression in the control group than in the experimental group, although IL-4 was visualized in the Leydig cells, undifferentiated spermatogonia, spermatocytes, elongated spermatids, and the mature sperm from both groups **(Fig. 1 IL-4)**.

The ACE was visualized in the round, elongated spermatids, and mature sperm from both groups. In the interstitium we found that there was higher ACE expression in the Leydig cells of the experimental group compared to the control group **(Fig. 1 ACE)**.

Immunoreactivity

Fig. 2 and **Table 2** present the analysis of the results of the mean distribution of CRP, IL-4, SAA and ACE immunopositivity cells per seminiferous tubules in the control and experimental groups.

Statistical analysis of CRP and IL-4 expression showed significantly higher valuer in the experimental group (Germ (p=0.004, p=0.003) and Leydig cells (p=0.02, p=0.053)) compared to control groups. The measured value for SAA also increased in Leydig cells (p=0.023), but we did not find a change in expression in Germ cells (control and experimental groups).

Expression of ACE was determined Germ and Leydig cells in the experimental group show a clear upward trend. Control cells positively +(++), but in the experimental group, the number of positive cells increased (+++).

DISCUSSION

Over the last decades, much attention has been paid to obesity as a causative factor for chronic low-grade inflammation. It is often accompanied by infections in the male reproductive tract, ultimately resulting in infertility.[18]

Data on infertility show that about 30% of all young men have impaired sperm performance, and by in vitro procedures the male factor causing infertility reaches 50%.[19] According to a large number of studies, the issue of increasing male infertility rates is mainly due to lifestyle changes.[3] Increasing attention is paid to nutrition as a major inflammatory factor. Studies have sought to determine the link between obesity and various diseases due to the immune system response and signalling pathways.[20] This binding is provided by various mediators, immune cells and adipocytes induced by obesity.

To our knowledge, this is the first study which combines analysis of the expression of pro-inflammatory and anti-inflammatory markers and compares control and inflammatory changes in the testis after high lipid diet with special focus on steroid-producing cells from the interstitium and on spermatogenic cell differentiation.

CRP and SAA are systemic inflammatory markers which are very attractive prognoses because they can be easily derived from routinely performed blood tests. However, their immunohistological manifestation in the testis is not well represented.

Obesity causes inflammation which increases the levels of the pro-inflammatory markers SAA and CRP which in turn correlate with an increase in the visceral fat.[21,22] In this study, we found an increased expression of both markers in the testicular interstitium. In the spermatogenic cells, we found an increased significance of CRP in the

Table 1. Changes in weight (g) of experimental animals, male Wistar rats fed control (D12450H) and highly lipid (D12451) diet

	n	Median (g)	Mean ±SD (g)	95% CI (g)	p-value (vs. group C)
Initially	50	145	145.42±15.263	141.47–149.36	
C group	25	294	295.88±31.881	269.22–322.53	
E group	25	367.50	360.13±23.296	340.65–379.60	<0.01

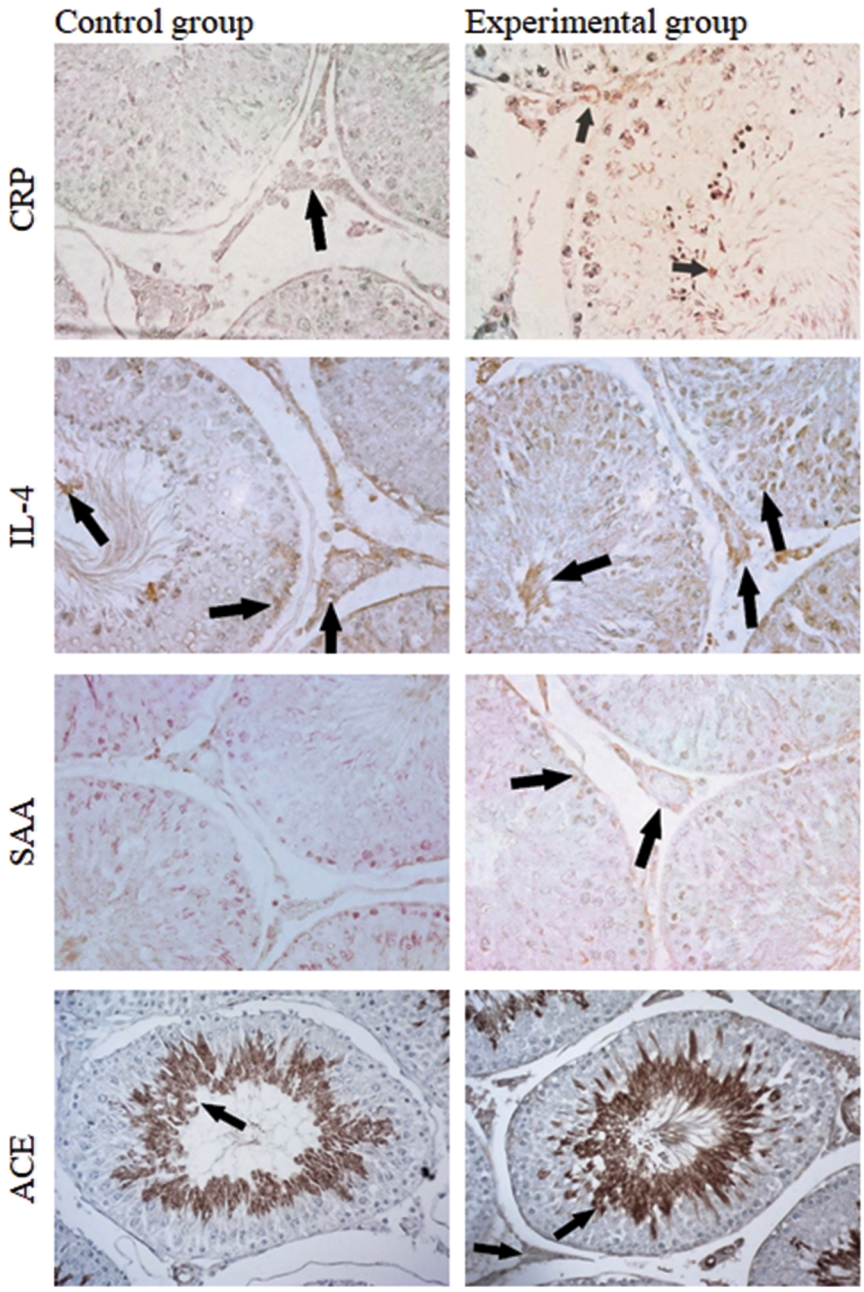

Figure 1. Distribution of immunoreactivity for CRP – it has an increased expression in the undifferentiated spermatogonia, round and elongated spermatids, head and tail of mature sperm and Leydig cells from group E compared to group C – visualised mainly in the steroid-producing cells in the interstitium; IL-4 had higher expression in the Leydig cells from the interstitium, the undifferentiated spermatogonia, spermatocytes, elongated spermatids, and the tail of mature sperm from group C compared to group E; SAA was predominantly expressed in the Leydig cells and undifferentiated spermatids from group E compared to the control group where it was not visualized. We found increased ACE expression in the round, elongated, and mature sperm from both groups. The ACE expression from group E was also found in the steroid-producing cells from the interstitium of the testes. E: experimental group; C: control group. (magnification ×400).

differentiating round and elongated spermatids, whereas in the manifestation of SAA, we did not detect any change.

CRP levels have been demonstrated to be elevated in the seminal plasma of patients with infection and chronic prostatitis.[23] The local inflammatory response is a physiological answer to an infection or injury that stimulates the immune system to produce an increased amount of inflammatory markers. During the acute phase, circulating concentrations of SAA and CRP could increase as much as 1000-fold.[24]

Recent studies associated elevated SAA levels with processes causing damage and tissue disorders.[25,26] Other studies found a correlation between the SAA levels in the blood and semen, but found no correlation between the

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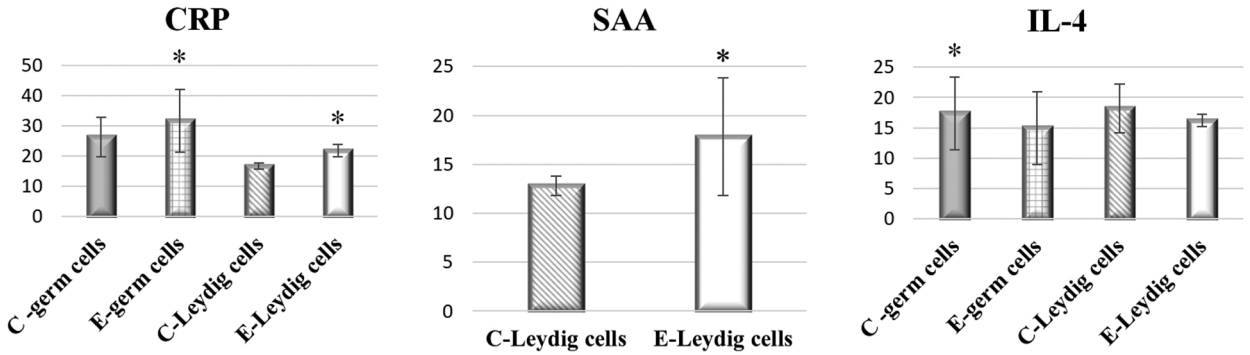

Figure 2. Distribution of immunoreactivity for CRP, SAA, IL-4, and ACE markers in spermatogenic cells and interstitial Leydig cells in the testis (control and experimental groups). The comparison is between the immunoreactivity of spermatogenic cell and interstitial cells in the testis from the two groups for each of the antigen types individually; n=25, mean ± SEM, *p<0.05.

Table 2. Statistical data of the measured immunoreactivity

Immunohisto-chemistry	Control group		Experimental group		p-value vs. germ cells	p-value vs. Leydig cells
	Germ cells±SD	Leydig cells±SD	Germ cells±SD	Leydig cells±SD		
CPR	26.41±6.5	16.6±1	31.7±10.5	21.8±2	p=0.04	p=0.003
IL-4	17.4±6	18.2±4	15±6	16.2±1	p=0.02	p=0.053
SAA	-	12.8±1	-	17.8±6	-	p=0.023
ACE	+++	+	+++	++	-	-

SAA levels in the seminal plasma and blood lymphocyte count. This shows that SAA is produced locally in the testes.[27] Our data on the predominant expression of serum amyloid A (SAA) in interstitium cells of the testis we associate with cytokine production, contribute to the pro-inflammatory state, reported in Hagihara.[28]

IL-4, secreted by activated Th2 lymphocytes, basophils, and mast cells, have pleiotropic functions such as induction of Th2 differentiation, immunoglobulin class switching, and B cell proliferation.[29] We believe that in the present study we demonstrated for the first time the new roles of IL-4 in the regulation of spermatogenesis through immunohistochemistry examination and semi-quantitative assessment, which prove the presence of expression in steroid-producing cells in the interstitium and the spermatogenic cell differentiation.

In obesity, cytokine expression was found to be higher, significantly correlated with adipometrics, particularly in obese participants.[29,30] Our results with respect to the expression of anti-inflammatory IL-4 showed higher values in the germinal cells and interstitium in the control group than in the experimental group. The detection of IL-4 also contributes to inflammation by incorporating alternative mechanisms into the testicular macrophages.[31] The role of IL-4 in the interstitium and the seminiferous epithelium in the testis is not well appreciated. Its increased expression in the seminiferous tubules is likely to be related to the main function of IL-4 differentiation and maturation of germ cells in the testis. The expression we found for IL-4 in the testicular interstitium can be suggested to be part of the immune regulatory factors that are secreted in the testis. IL-4, as part of the alternative anti-inflammatory system, is likely to participate in the immunosuppressive environment that is maintained in the healthy testis, provided by the coordinated influence of participants in this process such as the Leydig and the Sertoli cells, and macrophages toward an M2-like phenotype.[1,2,10]

Abdominal obesity is associated with insulin resistance. Adipose tissue expresses all the components of the RAS-signalling pathway and is involved in insulin resistance, possibly by effects on adipocyte differentiation.[32] In the testis ACE, RAS as part of the system, is represented by both isoforms testicular (tACE) and somatic (sACE). Our results supported that to the elevated expression of ACE in the round and elongated spermatids in both groups is associated with the manifestation of the testicular isoform of ACE. It takes part in the processes of maturation the sperm.[33] Testicular ACE expression levels increase with magnifying spermatogenic activity and decrease in oligospermic men.[34]

Studies using enzymatic activity and hybridization with cDNA probe have demonstrated the presence of renin, angiotensin-converting enzyme and its receptors in the interstitium in the testis.[35,36] ACE exerts its effects through its primary substrate Ang II, the effects of Ang II are expressed in inhibiting the function of Leydig cells, limiting the effect

of luteinizing hormone on the testis.[37] The influence of androgens on the differentiation of spermatogenic cells is considered crucial for controlling the process.[38] De Gendt et al.[39] found that androgen receptor knockout mice in Leydig cells were infertile with abnormal spermatogenesis and spermatogenic arrest in round spermatids[40].

Increased concentration of pro-inflammatory and anti-inflammatory markers in the spermatogenic epithelium and testicular interstitium inevitably leads to a change in its functionality. Reduced testosterone production has a negative effect on immunosuppression in the maintenance of immune tolerance in testis and is associated with a decrease in sperm concentration, motility, and sperm count.[41-43]

CONCLUSIONS

The study shows that obesity leads to inflammation in the male reproductive system, a risk factor for male infertility. This condition is triggered by the increased expression of inflammatory markers by adipocytes that infiltrate the testis, altering its immune-tolerant environment. These disorders impair the quality of sperm parameters and are a possible causative factor for the idiopathic infertility in men.

Ethical Approval

All methods used in the study were approved by the Scientific Ethics Committee at the Medical University of Plovdiv (No. P1041/25.04.2017) and the Bulgarian Agency for Food Safety (BAFS, No. 55/23.06.2016).

Acknowledgments

The research is funded by project NO 08/2015 of the Medical University of Plovdiv.

Conflict of Interest

None declared.

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Диета с высоким содержанием липидов и экспрессия провоспалительных маркеров в яичках

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Дата получения: 3 марта 2021 ♦ **Дата приемки:** 2 июня 2021 ♦ **Дата публикации:** 30 апреля 2022

Образец цитирования: Pencheva M, Koeva I, Dimitrov I, Daskalova E. High lipid diet and the expression of proinflammatory markers in testis. Folia Med (Plovdiv) 2022;64(2):288-295. doi: 10.3897/folmed.64.e65467.

Резюме

Введение: Ожирение определяется как хроническое слабовыраженное воспаление, являющееся проявлением клеточного ответа на различные стрессовые ситуации, приводящего к повреждению органов и тканей. Можно предположить, что диета с высоким содержанием липидов является пусковым механизмом развития воспалительных процессов, приводящих к нарушению иммунной толерантности в яичках.

Цель: Настоящее исследование направлено на демонстрацию экспрессии воспалительных маркеров в яичках на модели диеты с высоким содержанием липидов и возможное влияние на сперматогенез.

Материалы и методы: В исследовании использовали самцов крыс Wistar, разделённых на две группы: контрольную группу, получавшую стандартный корм для грызунов, и экспериментальную группу, получавшую корм с высоким содержанием липидов в течение 14 недель. Для исследования препаратов семенников были выполнены обычные гистологические методы, иммуногистохимические реакции на провоспалительные маркеры и морфометрический анализ.

Результаты: Диета с высоким содержанием липидов вызывала слабовыраженное воспаление яичка в опытной группе, что подтверждалось повышением провоспалительных маркеров: С-реактивного белка, сывороточного амилоида А и интерлейкина-4, а также повышением уровня ангиотензина -превращающий фермент в экспериментальной группе по сравнению с контрольной группой в экспериментальной модели на крысах.

Заключение: Наши результаты показывают, что диета с высоким содержанием липидов может быть возможной причиной идиопатического бесплодия у мужчин.

Ключевые слова

ACE, фертильность, IL-4, ожирение, SAA