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Original Article

# Impact of a High-fat Diet on the Development of Chronic Inflammation in Heart of Wistar rats

Iliyan V. Dimitrov[1], Vassil I. Kamenov[1], Nikolay P. Boyadjiev[2], Katerina N. Georgieva[2], Anelia V. Bivolarska[3], Milena N. Draganova-Filipova[4], Penka A. Angelova-Hristova[5], Slavi Delchev[6], Elena Daskalova[6], Fanka Gerginska[6], Teodora R. Stankova[3], Vilian Gramatikov[7]

[1] *Department of Chemistry and Biochemistry, Faculty of Pharmacy, Medical University of Plovdiv, Plovdiv, Bulgaria*
[2] *Department of Physiology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria*
[3] *Department of Chemistry and Biochemistry, Faculty of Pharmacy, Medical University of Plovdiv, Plovdiv, Bulgaria*
[4] *Department of Medical Biology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria*
[5] *Department of Physiology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria*
[6] *Department of Anatomy, Histology and Embryology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria*
[7] *Student at the Medical University of Plovdiv, Plovdiv, Bulgaria*

**Corresponding author:** Iliyan V. Dimitrov, Department of Chemistry and Biochemistry, Faculty of Pharmacy, Medical University of Plovdiv, 1A Perushtitza St., 4002 Plovdiv, Bulgaria; E-mail: idimitrov@meduniversity-plovdiv.bg; Tel: +359886013234

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**Introduction:** Obesity is linked to the development of low-grade, chronic inflammation. Obesity-related inflammation appears to be a different type of inflammation, mainly due to excessive food intake and unusual homeostasis. It can be evaluated by measuring the concentration of pro- and anti-inflammatory marker molecules – C-reactive protein (CRP), serum amyloid-A (SAA) and interleukin-4.

**Aim:** The aim of the present study is to evaluate the rate of the inflammatory process in heart, provoked by the consumption of a high-fat diet.

**Materials and methods:** Sixty 8-week-old male Wistar rats were used in this experiment. The laboratory animals were fed orally with two different types of rodent food for 14 or 18 weeks – a high-fat diet (experimental groups) and standard rodent food (control groups). They all were kept under standard housing conditions. The levels of the pro- and anti-inflammatory markers in tissue homogenates from heart were analyzed using ELISA. Their expression in tissue samples was detected immunohistochemically by the biotin-streptavidin-peroxidase method. The total protein concentration was determined by the Lawry method.

**Results:** CRP levels showed no significant differences when the control group was compared with the groups fed with a high-fat diet ($p>0.05$). The SAA levels detected were also insignificantly changed. Only the IL-4 tissue levels showed tendency to increase ($p<0.05$) in the high-fat diet group.

**Conclusions:** Our experiment indicates that there is a specific reaction of the heart to a high-fat diet. It also refers to the existence of adaptive mechanisms allowing the heart to counteract the development of dietary induced inflammation.

## Key words:

high-fat diet, low-grade inflammation, CRP, SAA, IL-4

## INTRODUCTION

Diet-induced obesity has become a significant medical and social problem because it is spread worldwide and associated with the development of disorders such as metabolic syndrome, insulin resistance, type 2 diabetes mellitus, high blood pressure and some cardiovascular diseases.[1,2]

Recently, diet-induced obesity has been linked to the development of low-grade chronic inflammation. This type of inflammation depends on the quality of the diet and differs from acute inflammation.[3,4] Obesity-related inflammation appears to be a different type of inflammation, mainly due to excessive food intake and unusual homeostasis.[4] Regardless of the agents that cause it and the molecular pathways involved, inflammation should be related to the processes associated with the restoration of functional and phenotypic homeostasis of the affected cells and tissues.[3,5]

The main participants in the development of an inflammatory process are the immune cells presented in the bloodstream as well as in various tissues and organs such as liver, adipose tissue, connective tissue, skeletal muscles, heart, etc. Macrophages are the most numerous of all types of immune cells in white adipose tissue and their number, location and phenotype are significantly altered in obesity.[6]

The rate of inflammation and its origin can be assessed by measuring the pro- and anti-inflammatory marker molecules. C-reactive protein (CRP) is an acute-phase protein, synthesized and secreted predominantly by hepatocytes in response to elevated levels of IL-6.[7] There is evidence that CRP can be synthesized and secreted by other cell types such as macrophages[8], smooth muscle cells[9] and adipocytes[10].

Similarly to CRP, serum amyloid-A (SAA) is an acute phase protein, secreted primarily by the liver. It takes place in the cholesterol efflux from peripheral tissues to the liver, and participates in the relationship between hypertrophied adipocytes and macrophages infiltrated into the adipose tissue.[11] Its expression, similarly to the expression of CRP, is regulated by the pro-inflammatory cytokines IL-6 and TNF-α.[12,13] In vivo, the production of SAA is also associated with infiltration of macrophages into the adipose tissue.[11]

Interleukine-4 (IL-4) aids the processes of tissue repair after inflammation. IL-4 stimulates fibroblasts to synthesize collagen and restore extracellular matrix.[14,15] In addition, IL-4 stimulates cellular proliferation of tissue macrophages[16] and provokes their anti-inflammatory state[17].

## AIM

The aim of the present study was to evaluate the rate of the inflammatory process in heart, provoked by the consumption of high-fat diet in rats.

## MATERIALS AND METHODS

This study has been given permission to use laboratory animals in experiments by the Bulgarian Food Safety Agency (BFSA) with license No 55/23.06.2016. It has been conducted in accordance with the ethical standards of Medical University of Plovdiv by a resolution of the University Ethic Committee No P-1041 of 25.04.2017.

Sixty 8-week-old male Wistar rats (weight range 130–180 g) were obtained from the University vivarium. They were randomly divided into five groups, 12 animals in each:

1. Control group (C), fed with standard rodent food (D12450H, Research Diets, Inc.) for 14 weeks.
2. Control group (CC), fed with standard rodent food for 18 weeks.
3. Experimental group (E), fed with a high-fat diet (D12451 – Research Diets, Inc.) that causes weight gain and metabolic syndrome manifestations,[18] including inflammation, for 14 weeks.
4. Experimental group (EE), fed with a high-fat diet for 18 weeks
5. Experimental group (EC), fed with a high-fat diet for 14 weeks, and thereafter fed with standard rodent food for 4 weeks.

The animals of all groups had free access to food and water. All animals were kept under standard housing conditions: living space - 350 $cm^2$, temperature - 22±2°C and 12/12 h light/dark photoperiod cycles. At the end of the experiment all of the animals fasted overnight, and then were treated with an overdose of the anesthetic ketamine (87.5 mg/kg)/xylazine (12.5 mg/kg) and decapitated via a guillotine for small rodents (HUGOSACHSELECTRON-ICD-79232 March F.R., Germany). Blood serum and tissue samples from heart were collected and immediately frozen at -18°C. Tissue samples were also placed in paraffin for immunohistochemical analysis.

On the day of analysis, the tissue samples used in ELISA were brought to room temperature and homogenized via mechanical homogenizer (Polytron) in 0.02M PBS with detergent Triton 100x added, pH-7.4. The ELISA test was performed according to the manufacturer recommendations (Rat high-sensitivity C-reactive protein ELISA kit, EMELCA Bioscience; Rat Serum amyloid-A, SAA ELISA kit, EMELCA Bioscience; IL-4 Rat ELISA kit, EMELCA Bioscience). Quantitative analyses were performed by an ELISA microplate reader (HumanReader). Total protein concentration of the samples was determined by the Lawry method.[19] The data collected were statistically processed using SPSS, v.19.0 (SPSS Inc., Chicago, IL, USA). The groups were compared using Kruskal-Wallis test for non-parametric data and are presented as median + interquartile range (IQR). Differences with $p<0.05$ were considered statistically significant. The Dunn's post hoc test was performed for those groups where statistical difference was found.

The levels of CRP, SAA and IL-4 in heart are presented as a ratio of the markers' concentration in the sample to the total protein concentration in the same tissue sample



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(ng CRP/mg Protein, ng SAA/mg Protein and pg IL-4/mg Protein).

The expression of the pro and anti-inflammatory molecules was examined using biotin-streptavidin-peroxidase method with universal BioSB mouse/rabbit polydetection kit. Polyclonal antibodies against CRP, SAA and IL-4 were used as primary antibodies. Reaction visualization was performed by DAB, and its intensity was evaluated by semi-quantitative scale; "+" – positive reaction in 25% of 100 counted cells; "++" – 50% of 100 counted cells; "+++" – intensive expression in 100% of the cells.

## RESULTS

### CRP levels in heart

The level of expression of CRP in heart samples of the control group detected by immunohistochemical analysis, was relatively weak (+). The number of the positive cells, in the group fed with the high-fat diet, was also low, and the expression of the marker was weak (+) (**Fig. 1**).

No statistically significant differences were found when the values measured for each of the experimental groups [ELISA, C-15.8 ng/mg, IQR (14.7-21.9); CC-15.7 ng/mg, IQR (15.2-17.7); E-19.9 ng/mg, IQR (13.3-21.8); EE-18.7 ng/mg, IQR (16.8-20) and EC-16.2 ng/mg, IQR (15.318.7)], were compared using the Kruskal-Wallis test, p=0.558. All data are presented in **Fig. 2.**

### SAA levels in heart

SAA expression in heart detected by immunohistochemical analysis is similar to the expression of CRP in the same organ. It was weak in both, the control group (+) and the group fed with a high-fat diet (+) (**Fig. 3**).

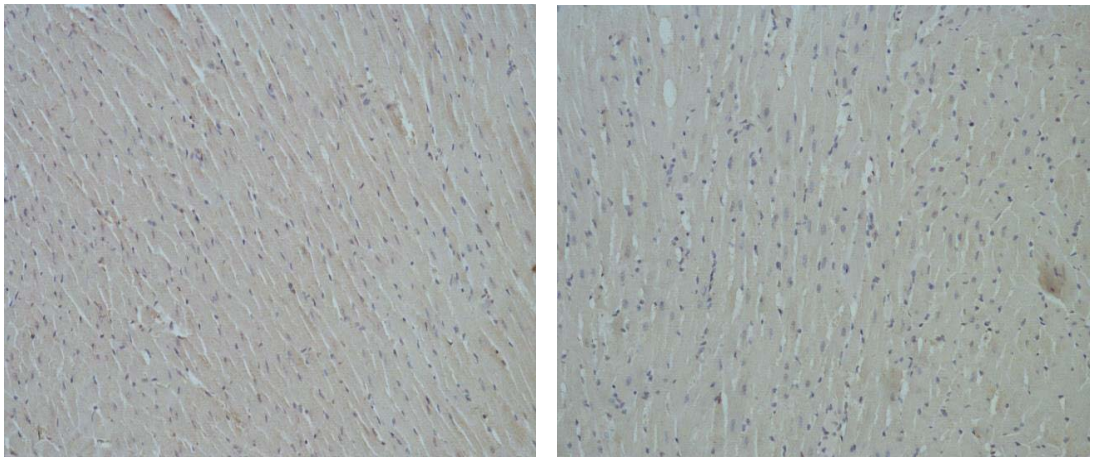

**Figure 1.** Microphotographs of the CRP expression in heart.

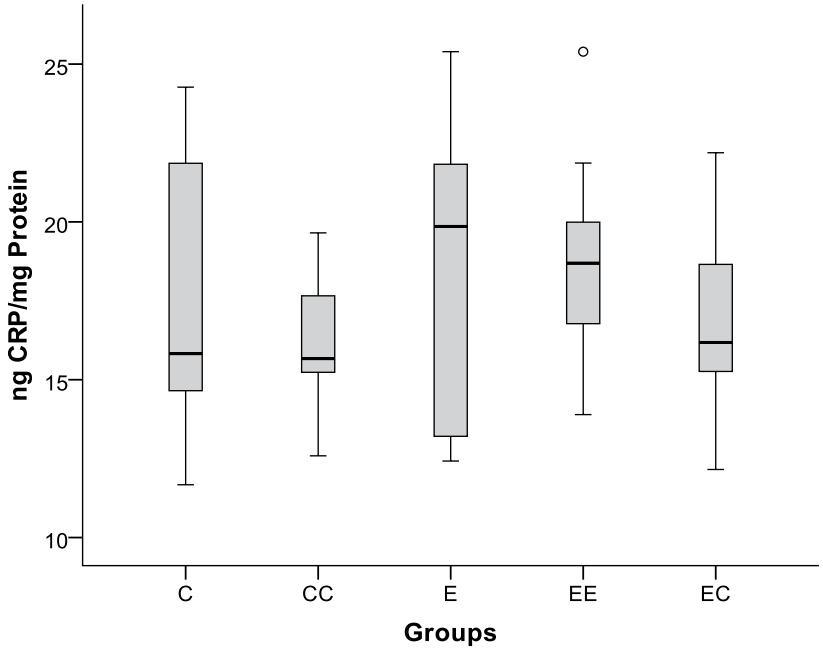


**Figure 2.** CRP levels in tissue homogenates from heart samples.

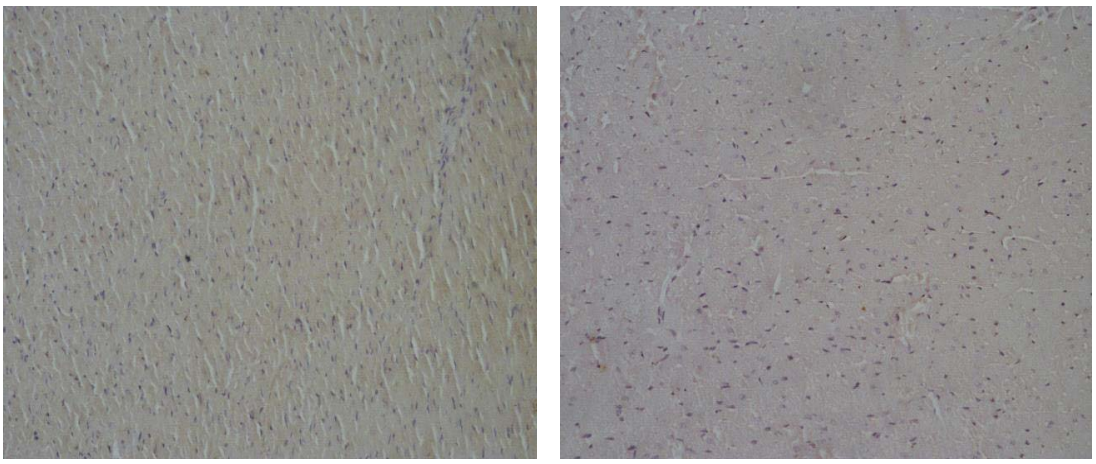

**Figure 3.** Microphotographs of the SAA expression in heart.

The quantitative ELISA method showed that the SAA levels remain a constant value across the groups, showing no significant differences. There was no statistical difference when the values obtained from all the experimental groups were compared [C-14.9 ng/mg, IQR (13.7-15.7); CC-14.6 ng/mg, IQR (14.5-15.4); E-14.7 ng/mg, IQR (14.02-18.9); EE-14.5 ng/mg, IQR (13.1-19.5) and EC-13.1 ng/mg, IQR (12.1-18.1), p=0.877]. All data are presented in **Fig. 4**.

### Changes in the IL-4 levels in heart

The IL-4 expression in heart measured immunohistochemically was weak similar to the expression of CRP and SAA. Unlike CRP and SAA, though, IL-4 expression in the control group (+) was significantly weaker than in the group fed with the high-fat diet (++) (**Fig. 5**).

Tissue IL-4 levels (ELISA) showed tendency to increase. IL-4 levels were significantly higher in the group fed with high-fat diet: E (20.9 pg/mg, IQR (18.5-23.4)) compared with control group (C-7.7 pg/mg, IQR (5.9-12.04), p=0.024). This difference was also detected when the control group (C) was compared with the group that had received high-fat diet for a longer period of time (EE-21.8 pg/mg, IQR (12.7-22.8), p=0.004).

The IL-4 tissue levels rapidly drop when the quality of the food was changed. The IL-4 was much lower in the group with the changed diet (EC-8.1 pg/mg, IQR (6.8-9.9)), compared with both groups fed only with high-fat diet, for the same period of time (EE), p=0.004, or the shorter period of time (E), p=0.023. On the other hand, the levels of IL-4 detected for the EC group were very similar to the

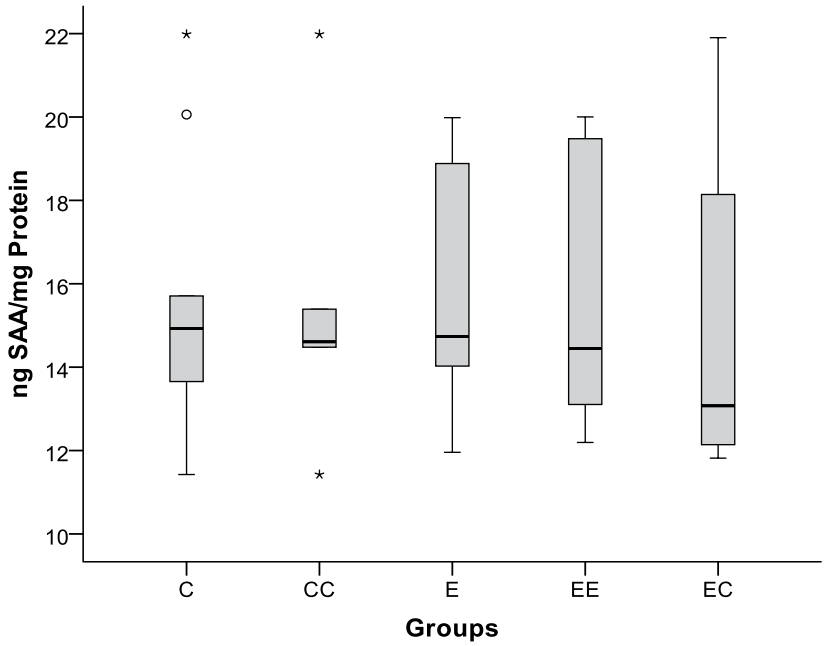


**Figure 4.** SAA levels in tissue homogenates from heart samples.

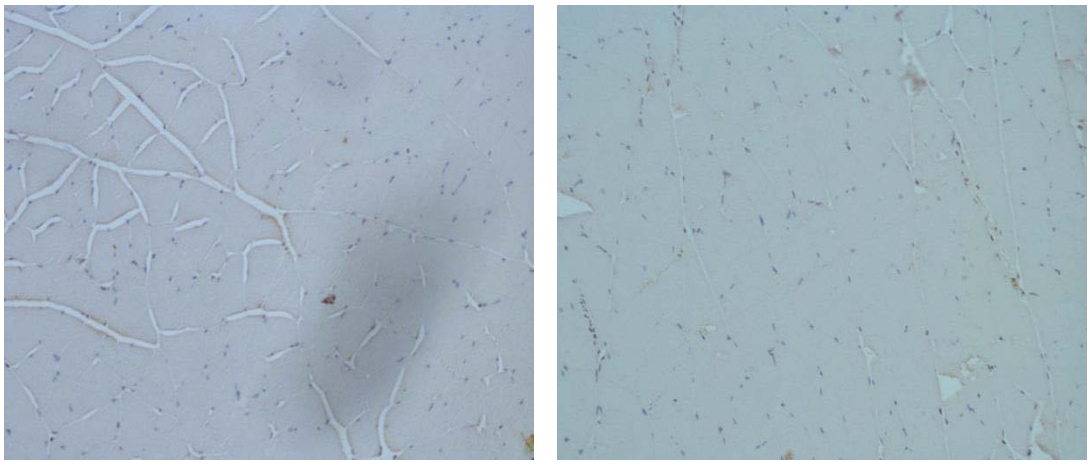

**Figure 5.** Microphotographs of the IL-4 expression in heart.

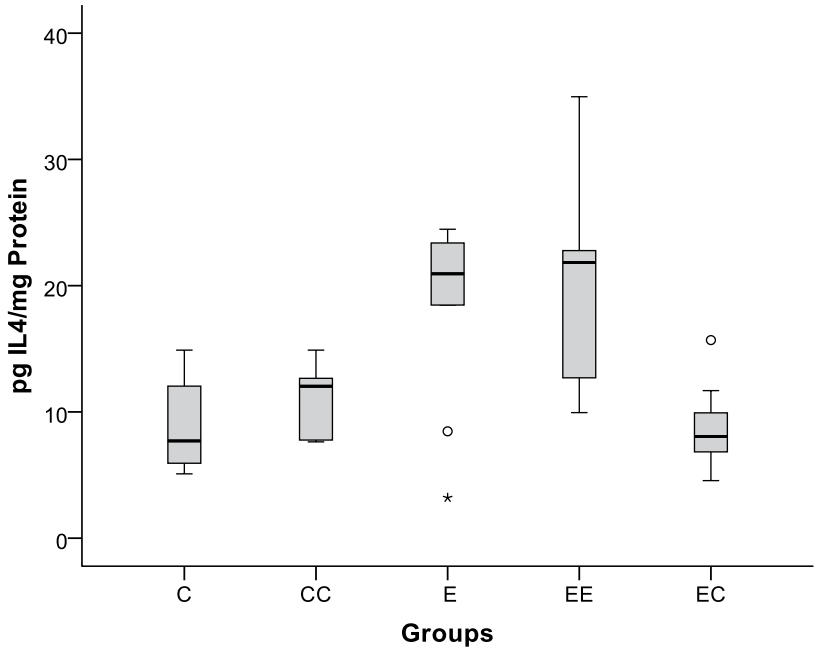


**Figure 6.** IL-4 levels in tissue homogenates from heart samples.

levels measured for the control groups at week 14, p=1.000, and at week 18 (CC-12.04 pg/mg, IQR (7.8-12.7), p=0.468). All data are graphically presented in **Fig. 6**.

## DISCUSSION

Adipose tissue (AT) depots that are anatomically attached to the heart (epicardial adipose tissue, EAT) and vessels are able to interact with their neighboring cells and tissues directly in a paracrine way, hence to regulate their metabolism under physiological and pathological conditions.[20,21] EAT possesses a phenotype closer to that of visceral AT.[22] Free fatty acids (FFA), normally reaching the myocardium via the coronary circulation, are a major source of energy in the heart. In a high-fat diet, EAT may act as an energy buffer, potentially protecting the myocardium from FFA overload.[23] Conversely, EAT may act as an excess source of FFA, which is potentially associated with myocardial dysfunction.[24] EPT, as well as the visceral AT, is linked to an increased risk of development of cardio-vascular diseases.[25]

CRP and SAA are acute phase proteins. They are secreted predominantly by the liver.[26] From hepatic synthesis and secretion during the acute phase of the inflammatory process, their synthesis and secretion become adipocytic in high-fat diet and obesity.[27,10] It has been reported that their secretion depends on the secretion of the pro-inflammatory TNF-α and IL-6.[28] Our experiment demonstrated lack of statistically significant changes in the levels of both CRP and SAA. It could be explained by the lack, or changed se-

cretion, of natural stimuli for their synthesis and secretion, namely, the change in the phenotype of tissue macrophages from M2 (non-classically activated) to M1 (classically activated). Classically activated macrophages express and secrete the pro-inflammatory molecules TNF-α and IL-6[28] that are required for the synthesis and secretion of CRP and SAA.

Despite the data of the development of an inflammatory reaction in the heart[29] our experiment did not demonstrate presence of such an inflammatory process. Neither CRP, nor SAA levels were significantly elevated. The rapid rise of the anti-inflammatory IL-4 levels during the experiment is indicative of presence of effective mechanisms for regulation of the inflammatory process. Further experiments are needed to demonstrate the existence of such mechanisms.

## CONCLUSION

Our experiment suggests that there is a specific reaction of the heart to a high-fat diet. Our previous experiment detected that the intake of a high-fat diet changes the concentration of the pro-inflammatory CRP and SAA molecules in blood, liver and adipose tissue,[30] and therefore for the development of chronic, low-grade inflammation in these tissues and organs. The absence of statistically significant changes of these markers in heart indicates for the higher degree of resistance of the heart to changes in the food intake. On the other hand, the statistically significant changes in the levels of anti-inflammatory IL-4 in the same organ suggest the existence of mechanisms that allow the heart to counteract the development of chronic low-grade inflammation.

## AKNOWLEDGMENTS

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# Влияние высококалорийной диеты на развитие хронического воспаления сердца у крыс породы Вистар

**Илиян В. Димитров[1], Васил И. Каменов[1], Николай П. Бояджиев[2], Катерина Н. Георгиева[2], Анелия В. Биволарска[3], Милена Н. Драганова-Филипова[4], Пенка А. Ангелова-Христова[5], Слави Делчев[6], Елена Даскалова[6], Фанка Гергинска[6], Теодора Р. Станкова[3], Вилиян Грамматиков[7]**

[1]Кафедра химии и биохимии, Факультет фармации, Медицинский университет- Пловдив, Пловдив, Болгария
[2]Катедра физиологии, Факультет медицины, Медицинский университет - Пловдив, Пловдив, Болгария
[3]Кафедра химии и биохимии, Факультет фармации, Медицинский университет - Пловдив, Пловдив, Болгария
[4]Кафедра медицинской биологии, Факультет медицины, Медицинский университет - Пловдив, Пловдив, Болгария
[5]Кафедра физиологии, Факультет медицины, Медицинский университет - Пловдив, Пловдив, Болгария
[6]Кафедра анатомии, гистологии и эмбриологии, Факультет медицины, Медицинский университет - Пловдив, Пловдив, Болгария
[7]Студент Медицинского университета-Пловдив, Пловдив, Болгария

**Адрес для корреспонденции:**
Илиян В. Димитров, Кафедра физиологии, Факультет медицины, Медицинский университет-Пловдив, ул. „Перущица" № 1, 4002 Пловдив, Болгария;

E-mail: idimitrov@meduniversity-plovdiv.bg;

Tel: +359886013234

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**Введение:** Ожирение связано с развитием хронического воспаления слабой степени. Связанное с ожирением воспаление является другим типом воспаления, главным образом, из-за чрезмерного потребления пищи и необычного гомеостаза. Его можно оценить путём измерения концентрации молекул про- и противовоспалительного маркера-С-реактивного белка (CRP), сывороточного амилоида-А (SAA) и интерлейкина-4 (IL-4).

**Цель:** Целью данного исследования является оценка частоты возникновения воспалительных заболеваний сердца, спровоцированных высококалорийной диетой.

**Материалы и методы:** В эксперименте использовали самцов крыс линии Вистар, в возрасте шестидесяти восьми недель. Лабораторных животных перорально кормили двумя различными типами корма для грызунов в течение 14 и 18 недель - высококалорийным рационом (экспериментальные группы) и стандартным кормом для грызунов (контрольные группы). Всех животных содержали в стандартных условиях обитания. Уровни про- и противовоспалительных маркеров в гомогенате тканей сердца анализировали методом ELISA. Их экспрессия в образцах тканей была иммуногистохимически установлена методом биотин-стрептавидин-пероксидазы. Общую концентрацию белка определяли методом Лаури.

**Результаты:** Уровни CRP не показали значительных различий при сравнении контрольной группы с группами с высоким содержанием липидов ($p > 0,05$). Измеренные уровни SAA также не имели статистически значимых изменений. Только уровни IL-4 в ткани имели тенденцию к увеличению ($p < 0,05$) в группе с высоким содержанием липидов.

**Выводы:** Наш эксперимент показывает, что существует специфическая реакция сердца на высококалорийную диету. Это также относится к наличию адаптивных механизмов, которые позволяют сердцу противодействовать развитию вызванного диетой воспаления.