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INFLUENCE OF ORGANISM STIMULATION WITH BACTERIAL LIPOPOLYSACCHARIDE ON THE METABOLISM OF THE EXTRACELLULAR MATRIX OF THE HEART OF RATS UNDER CONDITIONS OF EXPERIMENTAL METABOLIC SYNDROME

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Ключові слова: *метаболічний синдром, серце, бактеріальний ліпополісахарид, позаклітинний матрикс, глікозаміноглікани*

Abstract. Influence of organism stimulation with bacterial lipopolysaccharide on the metabolism of the extracellular matrix of the heart of rats under conditions of experimental metabolic syndrome. Akimov O.Ye., Mykytenko A.O., Kostenko V.O. *Until recently, the extracellular matrix was considered only a structural component of the organ, which performs exclusively the function of the framework. However, recent studies provide insight into a much broader role of extracellular matrix in metabolic homeostasis, the transmission of intra-organ and tissue signals. Metabolic syndrome and chronic infectious diseases can change the extracellular matrix's structure in the heart. However, the combined effect of bacterial lipopolysaccharide and metabolic syndrome on extracellular matrix of the heart remains insufficiently elucidated at present. The purpose of this work is to establish the effect of organism stimulation with bacterial lipopolysaccharide on the concentration of different fractions of glycosaminoglycans, the intensity of collagenolysis and the content of sialic acids in the heart of rats under conditions of experimental metabolic syndrome. The study was conducted on 24 sexually mature rats of the "Wistar" line weighing 200-260 g. Animals were divided into 4 groups with 6 animals in each group: control, metabolic syndrome group, lipopolysaccharide injection group and combination of lipopolysaccharide injection and metabolic syndrome group. Metabolic syndrome was modelled by using 20% fructose solution as the only water source. Lipopolysaccharide of S. typhi was administered according to the scheme: the first week, 0.4 μg/kg 3 times intraperitoneally, then once a week 0.4 μg/kg throughout the experiment. Experiment lasted for 60 days. The concentration of glycosaminoglycans, their separate fractions, the content of free L-hydroxyproline and sialic acids was studied in 10% rat heart homogenate. The combined effect of stimulation of the organism with bacterial lipopolysaccharide and metabolic syndrome modeling led to an increase in the total concentration of glycosaminoglycans in the heart of rats by 73.46% compared to the control group. Under these conditions, the concentration of the heparin-heparan fraction of glycosaminoglycans in the heart of rats increased by 188.64% compared to the control group. The content of the keratan-dermatan fraction of glycosaminoglycans increased by 75.34%, and the chondroitin fraction of glycosaminoglycans increased by 17.63%. The concentration of free L-hydroxyproline increased by 167.23%. The content of sialic acids increased by 66.95%. Metabolic syndrome, stimulation of the organism with bacterial lipopolysaccharide and their combination lead to intensification of degradation of the extracellular matrix of the heart of rats due to increased collagenolysis, destruction of proteoglycans and glycoproteins.*

Реферат. Вплив стимуляції організму бактеріальним ліпополісахаридом на метаболізм екстрацелюлярного матриксу серця щурів за умов експериментального метаболічного синдрому. Акімов О.Є., Микитенко А.О., Костенко В.О. *Екстрацелюлярний матрикс до недавнього часу вважався лише структурним компонентом органа, який виконує виключно функцію каркаса. Проте останні дослідження дають уявлення про значно ширшу роль екстрацелюлярного матриксу в метаболічному гомеостазі, передачі внутрішньоорганних та тканинних сигналів. Метаболічний синдром та хронічні інфекційні захворювання можуть змінювати структуру екстрацелюлярного матриксу в серці. Проте на цей час недостатньо з'ясованим залишається поєднаний вплив бактеріального ліпополісахариду та метаболічного синдрому на екстрацелюлярний матрикс серця. Метою цієї роботи є встановлення впливу стимуляції організму бактеріальним ліпополісахаридом на концентрацію різних*

фракцій глікозаміногліканів, інтенсивність колагенолізу та вміст сіалових кислот у серці щурів за умов експериментального метаболічного синдрому. Дослідження проведено на 24 статевозрілих щурах лінії «Вістар» масою 200-260 г. Тварини були розподілені на 4 групи по 6 тварин у кожній групі: контрольна, група метаболічного синдрому, група введення бактеріального ліпополісахариду та група поєднання метаболічного синдрому та введення бактеріального ліпополісахариду. Метаболічний синдром відтворювали шляхом використання 20% розчину фруктози в якості єдиного джерела води. Ліпополісахарид S. typhi вводили за схемою: перший тиждень 3 рази по 0,4 мкг/кг внутрішньоочеревинно, далі раз на тиждень по 0,4 мкг/кг внутрішньоочеревинно протягом усього експерименту. Експеримент тривав 60 діб. У 10% гомогенаті серця щурів досліджували концентрацію глікозаміногліканів, їх окремих фракцій, вміст вільного L-гідроксипроліну та сіалових кислот. Поєднаний вплив стимуляції організму бактеріальним ліпополісахаридом та метаболічного синдрому призводить до збільшення загальної концентрації глікозаміногліканів у серці щурів на 73,46% порівняно із контрольною групою. За цих умов концентрація гепарин-гепаранової фракції глікозаміногліканів у серці щурів зростає на 188,64% порівняно із контрольною групою. Вміст кератан-дерматанової фракції глікозаміногліканів зростає на 75,34%, а хондроїтинової фракції глікозаміногліканів збільшується на 17,63%. Концентрація вільного L-гідроксипроліну збільшується на 167,23%. Вміст сіалових кислот зростає на 66,95%. Моделювання метаболічного синдрому, стимуляція організму бактеріальним ліпополісахаридом та їх поєднання призводять до інтенсифікації деградації екстрацелюлярного матриксу серця щурів за рахунок посилення колагенолізу, деструкції протеогліканів та глікопротеїдів.

Extracellular matrix (ECM) and its individual components play a significant role in physiological and pathological processes. ECM forms a three-dimensional structure, which consists of macromolecules, such as: collagens, elastin, laminins and tenascins, proteoglycans and glycosaminoglycans, hyaluronan and their cellular receptors [1]. In recent years, scientists are paying more and more attention to the role of ECM in the processes of regulating the architecture of tissues and their regeneration after damage [2].

In the heart ECM also plays an important role in tissue homeostasis. The ECM not only provides structural support to cardiomyocytes, but also facilitates the transmission of force and key cell signals to cardiomyocytes, endothelial and interstitial cells [3]. Disturbance of the ECM structure in the dead body can lead to the development of heart failure both against the background of ischemic disease and without the influence of ischemia [3]. The ECM of the heart contains stem cells and progenitor cells of cardiocytes, which are an important pool of "reserve" cells that can be activated in the post-ischemic period to ensure complete regeneration of heart tissue after a heart attack (without the formation of a scar/fibrosis) [4]. Physiological disbalance between the processes of formation and degradation of ECM components in the heart can lead to the development of cardiac fibrosis [5].

Bacterial lipopolysaccharide (LPS) can lead to ECM remodeling due to NLRP3 inflammasome activation in adipose tissue [6]. The effect of bacterial LPS on ECM is controversial and depends on the organ. It was established that preconditioning of synovial cells using LPS leads to their formation of extracellular vesicles, which have an inhibitory effect on the degradation of ECM components in joints and are a potential therapeutic agent for the treatment of osteoarthritis [7]. Metabolic syndrome (MetS) and associated low-grade systemic inflammation can also affect ECM metabolism, as shown in our previous work [8].

Currently, the combined effect of organism stimulation with bacterial LPS and MetS on the processes of ECM degradation in the heart is not sufficiently studied.

The purpose of this work is to establish the effect of organism stimulation with bacterial lipopolysaccharide on the concentration of different fractions of glycosaminoglycans, the intensity of collagenolysis and the content of sialic acids in the heart of rats under conditions of experimental metabolic syndrome.

MATERIALS AND METHODS OF RESEARCH

The study was conducted on 24 sexually mature rats of the "Wistar" line weighing 200-260 g. The animals were divided into 4 groups of 6 animals in each group. The animals of the first group made up the control group. The animals of this group fed on the standard diet of the Poltava State Medical University vivarium and received an intraperitoneal injection of 0.9% sodium chloride solution in a volume of 0.1 ml twice a week for 60 days. The second group was the experimental metabolic syndrome (MetS) group. The animals of this group fed on a standard diet, but they received a 20% fructose (D-fructose, ADM, Turkey) solution (as the only source of drinking water and received an intraperitoneal injection of 0.9% sodium chloride solution in a volume of 0.1 ml twice a week for 60 days [9]. The third group was the group of organism stimulation with bacterial LPS (LPS group). The animals of this group fed on a standard diet and for 60 days received an injection of bacterial LPS *S. typhi* (Pyrogenal, Medgamal) according to following scheme: on the first week 0.4 μg/kg of bacterial LPS was introduced by intraperitoneal injection three times a week, then once a week for the rest of the experiment (60 days) [8]. The fourth group was the group of the combined

effect of organism stimulation with bacterial LPS and modeling of MetS (LPS+MetS group). The animals of this group fed on a standard diet, received a 20% fructose solution as the only source of drinking water and an injection of bacterial LPS of *S. typhi* according to abovementioned scheme [8, 9].

The principles and recommendations set forth in the Law of Ukraine "On the Protection of Animals from Cruel Treatment" and in the "Bioethical Examination of Preclinical and Other Scientific Research Performed on Animals" were taken into account. All manipulations with laboratory animals were approved by the Bioethics Commission of the Poltava State Medical University (Protocol No. 206 dated 24.06.2022). This work is a part of Scientific Research Work of department of Pathophysiology of Poltava State Medical University (State registration No. 0119U103898).

Animals were removed from the experiment under following procedure: 1. Animals were injected intraperitoneally with sodium salt of thiopental at a dose of 50 mg/kg (Rotex Medica, Germany). 2. After confirmation of absence of corneal reflexes the incision of thorax in order to reach heart was made. 3. Blood sampling from the right ventricle of the heart in order to simulate death from major blood loss was performed.

The object of the study was 10% rat heart homogenate, which was prepared using 0.2 M Tris buffer solution (pH=7.4). In order to prepare tissue homogenate rat heart was washed with 0.9% sodium chloride solution to remove blood, then ventricles were separated with scissors and washed again with 0.9% sodium chloride solution. Afterwards, ventricles were weighted. For tissue homogenate exactly 1 g of heart ventricle tissue was used, it was cut with scissors into small pieces, then it was grinded in porcelain mortar with porcelain pestle. Afterwards 9 ml of 0.2 M Tris buffer solution (pH=7.4) were added. Contains of porcelain mortar were vigorously mixed with pestle. Then the contains of porcelain mortar were transferred to centrifuge tube. Obtained mixture of tissue and 0.2 M Tris buffer solution (pH=7.4) was centrifugated at 3000 g for 10 minutes. Upper layer of obtained centrifugate was moved to new centrifuge tube and then used for biochemical analysis.

The total concentration of glycosaminoglycans (GAG), the concentration of heparin-heparan, keratan-dermatan and chondroitin fractions of GAG, the concentration of free L-hydroxyproline and the concentration of sialic acids were determined spectrophotometrically in 10% rat heart homogenate [8]. All spectrophotometric studies were performed on spectrophotometer Ulab 101, on which we estimated the absorbance (A) of the sample on specified according to biochemical method wavelength (λ). Received absorbances were then used for calculation of concentrations of above mentioned components of connective tissue.

The obtained results were processed using the methods of mathematical statistics. Statistical processing was carried out using the Microsoft Office Excel program package and its Real Statistics 2019 extension developed by Charles Zaiontz (License CC BY 4.0). To determine the statistical significance of differences between groups, non-parametric analysis of variance was used using the Khruskal-Wallis method followed by pairwise comparisons using the Mann-Whitney U-test [10]. To avoid error in multiple comparisons, Bonferroni correction was used [10]. The difference between the studied groups was considered statistically significant at $p<0.05$. In the table, data were presented in the form of mean and standard error (M±SE).

RESULTS AND DISCUSSION

In our previous studies, it was shown that the use of a 20% fructose solution as the only source of drinking water against the background of a standard food diet led to the development of changes in the body of rats that are characteristic of the metabolic syndrome, namely: the development of hyperglycemia, hyperlipidemia, dyslipidemia (with a predominance low-density lipoproteins), hypercholesterolemia, and insulin resistance [8].

MetS modeling led to an increase in the total concentration of GAG by 56.17% compared to the control group of rats (Table). The concentration of the heparan-heparin fraction increased by 59.83% compared to the control group of rats. The concentration of keratan-dermatan fraction increased by 217.87%. The concentration of the chondroitin fraction decreased by 34.89%. The concentration of free L-hydroxyproline and sialic acids increased by 60.04% and 30.81%, respectively.

Therefore, under the conditions of MetS modeling by adding to the standard diet a 20% solution of fructose as the only source of drinking water, an increase in the intensity of collagenolysis and desialylation in the heart of rats was observed. Under these conditions, the concentration of GAG also increased due to the increase in the keratan-dermatan fraction and the heparin-heparan fraction of GAG. However, MetS modeling reduced the content of the chondroitin fraction of GAG in the heart of rats.

Stimulation of the organism with bacterial LPS led to an increase in the total concentration of GAG by 46.91% compared to the control group of rats. The concentration of the heparan-heparin fraction increased by 236.57% compared to the control group of rats. The concentration of keratan-dermatan fraction did not

change statistically significantly. The concentration of the chondroitin fraction decreased by 16.19%. The concentration of free L-hydroxyproline and sialic acids increased by 125.16% and 43.55%, respectively.

Comparing parameters of the MetS group and the group of stimulation of the organism with bacterial LPS, a decrease in the total concentration of GAG by 5.93% in the group of stimulation with bacterial LPS compared to MetS group was noted. Stimulation of the organism with bacterial LPS increased the content of the heparin-heparan fraction of GAG by 110.57%, decreased the concentration of the keratan-dermatan fraction of GAG by 68.75%, increased the content of the chondroitin fraction of GAG by 28.73%, and led to an increase in the content of free L-hydroxyproline by 40.69%, but did not affect the content of sialic acids compared to the MetS group.

Parameters of the extracellular matrix degradation in the heart of rats under the condition of metabolic syndrome modeling and stimulation of the organism with bacterial lipopolysaccharide (M±SE)

Parameters	Groups			
	control, n=6	MetS, n=6	LPS, n=6	LPS+MetS, n=6
GAG concentration, µmol/l				
Total	**1.62±0.01**	**2.53±0.01***	**2.38±0.02*/#**	**2.81±0.07 */#/^**
Heparin-heparan fraction, µmol/l	**0.361±0.005**	**0.577±0.009***	**1.215±0.007*/#**	**1.042±0.005*/#/^**
Keratan-dermatan fraction, µmol/l	**0.442±0.006**	**1.405±0.010***	**0.439±0.010 #**	**0.775±0.012*/#/^**
Chondroitin fraction, µmol/l	**0.834±0.012**	**0.543±0.005***	**0.699±0.013 */#**	**0.981±0.004*/#/^**
Concentration of free L-hydroxyproline, µmol/g	**0.473±0.008**	**0.757±0.046***	**1.065±0.024*/#**	**1.264±0.017*/#/^**
Concentration of sialic acids, mg/g	**5.81±0.03**	**7.60±0.33***	**8.34±0.19***	**9.70±0.17*/#/^**

Notes: * – the data are statistically significantly different from the control group ($p<0.05$); # – the data are statistically significantly different from the experimental metabolic syndrome group ($p<0.05$); ^ – the data are statistically significantly different from the group of organism stimulation with bacterial lipopolysaccharide ($p<0.05$).

Thus, under the conditions of stimulation of the organism with bacterial LPS, an increase in the intensity of collagenolysis and desialization in the heart of rats was observed. Under these conditions, the concentration of GAG increased due to the increase in the heparin-heparan fraction of GAG. However, stimulation of the organism with bacterial LPS reduced the content of the chondroitin fraction of GAG in the heart of rats.

The combined effect of stimulation of the organism with bacterial LPS and MetS modeling led to an increase in the total concentration of GAG in the heart of rats by 73.46% compared to the control group. Under these conditions, the concentration of the heparin-heparan fraction of GAG in the heart of rats increased by 188.64% compared to the control group. The content of the keratan-dermatan fraction of GAG increased by 75.34%, and the chondroitin fraction of GAG increased by 17.63%. The concentration of free L-hydroxyproline increased by 167.23%. The content of sialic acids increased by 66.95%.

Comparing the data in the group of the combined effect of stimulation of the organism by bacterial LPS and MetS with the indicators of the MetS group, we found that the total concentration of GAG in the heart of rats increased by 11.07% compared to the indicators of the MetS group. The concentration of heparin-heparan and chondroitin fractions of GAG increased by 80.59% and 80.66%, respectively, when compared with the MetS group. However, the concentration of the keratan-dermatan fraction decreased by 44.84% compared to the MetS group. Concentrations of free L-hydroxyproline and sialic acids increased by 66.97% and 27.63%, respectively.

The combined effect of stimulation of the organism with bacterial LPS and MetS led to an increase in the total concentration of GAG in the heart of rats by 18.07% compared to the group of stimulation of the organism with bacterial LPS. The concentration of the heparin-heparan fraction of GAG in the heart of rats decreased by 14.24% compared to the group of stimulation of the organism with

bacterial LPS. The content of the keratan-dermatan fraction of GAG increased by 76.54% compared to LPS group, and the chondroitin fraction of GAG elevated by 40.34% compared to LPS group. The concentration of free L-hydroxyproline increased by 18.69% compared to LPS group. The content of sialic acids increased by 16.31% compared to LPS group.

Therefore, the combined effect of stimulation of the organism by bacterial LPS and MetS led to the highest level of intensification of the processes of collagenolysis and desialization in the heart of rats and increased the content of the chondroitin fraction of GAG.

MetS is accompanied by the activation of the transcription factor NF-κB. This factor has transcriptional control of matrix metalloproteinases, which may lead to the increase in the intensity of collagenolysis in the heart, which is observed in our study [11, 12]. Bacterial LPS can also activate the transcription factor NF-κB by interacting with Toll-like receptor 4 (TLR-4) [13]. The mechanisms underlying the activation of the transcription factor NF-κB in the development of MetS and the stimulation of the organism by bacterial LPS are different. Activation of the transcription factor NF-κB creates conditions for enhancement of matrix metalloproteinases activation, which are controlled by NF-κB. Possible synergetic effect of LPS and MetS on NF-κB activation may underlie collagenolysis intensification observed in our study.

Bacterial LPS can increase the content of sialic acids by increasing the activity of neuraminidase, which leads to the cleavage of N-acetylneuraminic acid residues from tissue proteoglycans [14]. Activation of neuraminidase is mediated by the effect of bacterial LPS on TLR-4 [15]. The scientific literature presents data on an increase in the concentration of sialic acids in the blood of patients with type II diabetes, which is a complication of the metabolic syndrome [16]. However, the mechanisms of increasing the content of sialic acids in the blood of patients with metabolic syndrome or type II diabetes remain unclear. Taking into account that the activation of neuraminidase under the conditions of exposure to bacterial LPS on the body is mediated by TLR-4, the participation of the transcription factor NF-κB in the processes of desialization under the conditions of MetS development cannot be ruled out.

An increase in the concentration of the heparin-heparan fraction of GAG under the conditions of stimulation of the organism with bacterial LPS may be a consequence of the activation of heparinase-3 under the influence of LPS [17]. A similar situation is observed in the conditions of sepsis, which can be considered as a highly intense systemic inflammatory process [18]. Under the conditions of MetS, the development of systemic inflammation of low intensity is often observed, which can also be the reason for the increase in the concentration of the heparin-heparan fraction of GAG in the heart of rats [18]. Considering the fact that heparan sulfate has potent anti-inflammatory properties, an increase in the concentration of the heparin-heparan fraction of GAG under conditions of MetS, stimulation of the organism by bacterial LPS and their combination can be considered as an adaptive response to the development of systemic inflammatory processes in the body [19].

An increase in the concentration of the keratan-dermatan fraction of GAG in the heart of rats under conditions of MetS may be associated with an increase in the level of endocan in the heart, which is supported by the results of Aleksandra Klisic and Dimitrios Patoulias [20]. An increase in the keratan-dermatan fraction of GAG is also observed during sepsis [21]. The lack of effect of stimulation of the body with bacterial LPS on the concentration of the keratan-dermatan fraction of GAG in our study can be explained by the low intensity of the systemic effect of LPS at a dose of 0.4 μg/kg.

Chondroitin sulfate has anti-inflammatory properties under the conditions of exposure of organism to bacterial LPS [22, 23]. Chondroitin sulfate also exhibits similar properties of relatively low-intensity inflammation, which is observed under conditions of type II diabetes [24]. Therefore, the decrease in the concentration of chondroitin sulfate fraction of GAG in the heart under the conditions of metabolic syndrome modeling (in MetS group) and stimulation of the organism with bacterial LPS (in LPS group) can be considered as a negative phenomenon arising from insufficient activation of adaptive systems. An increase in the concentration of the chondroitin fraction of GAG under the conditions of the combined effect of MetS and stimulation of the organism with bacterial LPS (in LPS+MetS group) may be a consequence of the maximum stress of the adaptive systems of the heart.

Disbalance between different connective tissue components, which compose the backbone of ECM in different organs may be the result of inadequate production of various regulatory compounds like nitric oxide [25, 26]. From the other hand, during metabolic syndrome and injection of organism with bacterial LPS, activation of proinflammatory cascades with subsequent excessive production of reactive oxygen and nitrogen species may also underlie observed changes in ECM of heart and require further study. A perspective approach to treatment of observed changes in heart ECM during metabolic syndrome may be the usage of polyphenolic compounds like resveratrol and quercetin [27].

CONCLUSIONS

1. Metabolic syndrome, stimulation of the organism with bacterial lipopolysaccharide and their combination lead to intensification of degradation of the extracellular matrix of the heart of rats due to increased collagenolysis, destruction of proteoglycans and glycoproteins.
2. The combination of metabolic syndrome and stimulation of the organism with bacterial lipopolysaccharide has a synergistic effect on collagen degradation and desialization processes in the heart of rats.

Contributors:

Akimov O.Ye. – conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, writing – original draft, writing – review & editing;

Mykytenko A.O. – conceptualization, investigation, methodology, resources, validation, writing – review & editing;

Kostenko V.O. – conceptualization, data curation, project administration, resources, supervision, validation, writing – review & editing.

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