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Influence of bacterial lipopolysaccharide on the degradation of the components of the extracellular matrix of rat biceps femoris muscle during high fructose diet-induced metabolic syndrome

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Metabolic syndrome is an epidemic of non-infectious origin, which is associated with the consumption of a large amount of high-calorie food and a sedentary lifestyle. It is not excluded that bacterial lipopolysaccharides (LPS) may enter the body during metabolic syndrome. The purpose of this work is to study the combined effect of bacterial lipopolysaccharide and high fructose diet on the concentration of glycosaminoglycans and their individual fractions, the content of free L-oxyproline and sialic acids in rat biceps femoris muscle. Bacterial LPS was injected intraperitoneally at a dose of 0.4 μg/kg. Metabolic syndrome was modelled by using 20% fructose solution as only source of drinking water. In the test group of animals total concentration of glycosaminoglycans increased by 22.53%, the heparin-heparan and keratan-dermatan fraction concentrations raised by 26.18 and 35.91%, but concentration of the chondroitin fraction did not change compared to the control. The concentrations of free L-oxyproline and sialic acids increased by 120.71 and 156.78%, respectively. Thus, high fructose diet, stimulation of the organism with bacterial lipopolysaccharide and their combination lead to increased degradation of glycoproteins and proteoglycans and intensify collagenolysis in the biceps femoris muscle of rats.

Key words: metabolic syndrome; bacterial lipopolysaccharide; L-oxyproline; glycosaminoglycans; sialic acids; biceps femoris.

INTRODUCTION

In most scientific sources, components of the extracellular matrix of muscles (ECMM) are considered as exclusively structural elements that have practically no metabolic function, but only eliminate friction during contraction and myofibril bundle retention. However, recent researches show that ECMM also contributes to the maintenance of physiological metabolic activity and muscle regeneration [1]. Under the conditions of excessive activation of cyclooxygenase-2 (COX-2) in ECMM fibroblasts, the development of fibrosis and muscle atrophy is possible [2]. Therefore, ECMM components should be considered as metabolically active substances.

Infectious agents accompany humanity throughout its history. Therefore, there is an evolutionarily determined cellular response to most bacterial lipopolysaccharides (LPS), mediated by Toll-like receptors (TLRs) and activation of nuclear transcription factor κB (NF-κB) [3]. At the same time, in recent decades humanity faced a new non-infectious pandemic - the metabolic syndrome (MetS), which arose as a result of the socio-economic development of society and elimination of hunger in most economically stable countries. MetS occurs as a consequence of consuming an excessive amount of calories (much more than the sum of calories needed for basic metabolism and labor costs) and is also accompanied by the transcription factor NF-κB activation [4].

Activation of the transcription factor NF-κB can affect metabolic and structural changes

in the connective tissue of various organs and systems. In the ECMM, this factor can induce cell apoptosis and cause the breakdown of non-cellular components [5, 6]. Several matrix metalloproteinases (MMPs) that can cleave collagen fibers are under the direct transcriptional control of NF-κB [7].

Increased collagenolisis (collagen degradation) due to elevated activities of MMPs in ECMM can lead to inflammatory myopathies (myositis, polymyositis, and dermatomyositis) [8]. Decreased intensity of collagen degradation can lead to development of fibrotic changes in muscles similar to those observed in Duchenne muscular dystrophy [9]. Therefore, L-oxyproline concentration can be used as a viable marker of muscle homeostasis. Such components of ECMM as proteoglycans and glycosaminoglycans (GAG) also have a significant impact on muscle homeostasis. For instance, glypican, a heparan sulfate proteoglycan, regulates Wnt and Hedgehog intracellular signalling routes in muscles [10]. Therefore, changes in concentrations of heparin-heparan, keratan-dermatan or chondroitin fractions of GAG can affect muscle metabolism and function.

Since stimulation of the organism with bacterial lipopolysaccharides and MetS can potentially activate the transcription factor NF-κB, these effects can lead to the degradation of ECMM elements. However, the specifics of their combined effect on the ECMM metabolism remains insufficiently studied.

The purpose of this work is to study the combined effect of bacterial lipopolysaccharide and metabolic syndrome on the concentration of glycosaminoglycans and their individual fractions, the content of free L-oxyproline and sialic acids in the biceps femoris muscle of rats.

METHODS

The study was conducted on 24 male Wistar rats weighing 200-260 g. The animals were divided into 4 groups (by 6 each). Animals in the control group received manipulations similar to those from other groups, but they were injected with a 0.9% solution of sodium chloride instead of the active substance. In the second group, we reproduced MetS by using a 20% fructose solution as the only source of water for 60 days [11]. Animals in the third group were stimulated with bacterial LPS of *S. typhi* according to the following scheme: in the first week, the animals were administered LPS at a dose of 0.4 μg/kg intraperitoneally three times a week, then LPS was administered at a dose of 0.4 μg/kg intraperitoneally once a week throughout the experiment (60 days) [12]. The fourth group was a group of combined effects of LPS stimulation and MetS: the animals received fructose solution and they were administered LPS according to the scheme of group 3.

The animals were kept in the vivarium of Poltava State Medical University under standard conditions. When working with animals, we adhered to the "European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes". The animals were removed from the experiment under thiopental anesthesia by taking blood from the right ventricle. A day prior removal from the experiment animals were deprived from food in the evening.

The objects of the study were a 10% homogenate of rat biceps femoris muscle and blood samples from right ventricle. In 10% homogenate, the total concentration of GAG and the concentration of heparin-heparan, keratan-dermatan and chondroitin fractions of GAG were determined [13, 14]. The method of differential precipitation according to N. Volpi was used to determine the concentration of individual fractions of GAG. Normal isopropyl alcohol (propanol-1) was used as a precipitant [13, 14]. Also, the concentrations of free L-oxyproline and sialic acids were determined in the homogenate [15].

In the blood samples, we studied concentration of following metabolic substances: glucose, triglycerides (TG), total cholesterol (TC), cholesterol from low-density lipoproteins (LDL-C)

and cholesterol from high-density lipoproteins (HDL-C). All abovementioned substances were evaluated by respective assays produced by "Filisit Diagnostics" (Ukraine).

In order to evaluate development of insulin resistance we calculated following indexes.

Triglyceride and glucose (TyG) index. TyG = Ln(Glucose·TG-2) [16].

Triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio. TG/HDL-C = TG-HDL-C [16].

Statistical significance of the difference between groups was determined using the non-parametric Kruskal-Wallis analysis of variance method, followed by pairwise comparisons using the Mann-Whitney U-test. The difference was considered statistically significant at $P < 0.05$.

RESULTS AND DISCUSSION

Introduction of a 20% fructose solution as only source of drinking water led to increase in blood glucose level by 2.12 times, elevated TG and TC by 3.06 and 1.50 times, respectively, LDL-C increased by 1.65 times, and HDL-C decreased by 1.44 times compared to control group (Table 1). TyG and TG/HDL-C indexes increased by 1.24 and 4.39 times, respectively. These changes indicate presence of MetS in animals, which received a 20% fructose solution as only source of drinking water, as evidenced by hyperglycemia, hyperlipidemia, dyslipidemia and development of insulin resistance.

Administration of bacterial LPS led to increase in blood glucose level by 1.50 times, elevated TG and TC by 1.84 and 1.20 times, respectively, LDL-C increased by 1.27 times, and HDL-C decreased by 1.10 times compared to control group. TyG and TG/HDL-C indexes increased by 1.13 and 2.0 times, respectively. These changes indicate presence of MetS in LPS stimulation group, as evidenced by hyperglycemia, hyperlipidemia, dyslipidemia and development of insulin resistance.

Combination of introduction of a 20% fructose solution as only source of drinking water and stimulation with LPS led to increase in blood glucose level by 2.52 times, elevated TG and TC by 3.73 and 1.77 times, respectively, LDL-C increased by 2.20 times, and HDL-C decreased by 1.68 times compared to control group. TyG and TG/HDL-C indexes increased by 1.28 and 6.21 times, respectively. These changes indicate presence of MetS in animals of the combined group, as evidenced by hyperglycemia, hyperlipidemia, dyslipidemia and development of insulin resistance.

Modelling of MetS led to an increase in the total concentration of GAG in the homogenate of rat biceps femoris muscle by

Table 1. Metabolic changes in rat blood samples and insulin resistance indexes under conditions of metabolic syndrome and stimulation with bacterial lipopolysaccharide (M ± m; n = 6)

Parameters	Groups			
	Control	MetS	LPS	LPS + MetS
Glucose, mg/dl	70.02±1.10	148.30±1.99*	105.28±1.57*,**	176.26±0.52*,**,***
TG, mg/dl	79.30±5.06	243.09±4.96*	146.00±4.05*,**	295.71±2.98*,**,***
TC, mg/dl	45.64±0.55	68.32±0.94*	54.93±0.47*,**	80.71±0.42*,**,***
LDL-C, mg/dl	6.48±0.19	10.66±0.58*	8.21±0.11*,**	14.25±0.25*,**,***
HDL-C, mg/dl	21.38±0.60	14.83±0.38*	19.44±0.25*,**	12.74±0.38*,**,***
TyG	7.92±0.07	9.80±0.02*	8.94±0.03*,**	10.17±0.01*,**,***
TG/HDL-C	3.75±0.33	16.48±0.75*	7.52±0.26*,**	23.28±0.55*,**,***

Note: *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 stimulation with bacterial lipopolysaccharide ($P < 0.05$).

37.36% compared to the control (Table 2). Under these conditions, the heparin-heparan fraction concentration of GAG decreased by 45.94%. The concentration of keratan-dermatan and chondroitin fractions increased by 28.19 and 153.19%, respectively, when compared with the control. The concentrations of free L-oxyproline and sialic acids increased by 86.43 and 74.96%, respectively. Thus, simulation of MetS increases the breakdown of glycoproteins and proteoglycans in muscles, simultaneously increasing the intensity of collagenolysis. At the same time, under the conditions of MetS, there is a redistribution of the concentration of individual GAG fractions, which is accompanied by a decrease in the concentration of the heparin-heparan fraction and an increase in the content of keratan-dermatan and chondroitin fractions.

Bacterial lipopolysaccharide administration led to an increase in the total content of GAG in the homogenate of rat biceps femoris muscle by 39.56% compared to the control group. The heparin-heparan and chondroitin fraction of GAG concentrations increased by 69.76% and 20.42%, respectively, against the background of the absence of statistically significant changes in the keratan-dermatan fraction concentration. The concentrations of free L-oxyproline and sialic acids increased by 100.5% and 55.14%, respectively, compared to the control. Therefore, stimulation with LPS also leads to increased breakdown of glycoproteins and proteoglycans and intensification of collagenolysis in muscles. However, the redistribution of individual fractions of GAG has a different dynamic: the heparin-heparan and chondroitin fractions of GAG concentrations increase.

When comparing the indicators, we observed a slight (by 1.6%) but statistically significant increase in the total GAG concentration under LPS stimulation conditions compared to MetS. The heparin-heparan fraction of GAG concentration in the LPS group was 3.14 times higher than that in the MetS group. At the same time, the keratan-dermatan and chondroitin fraction concentrations were reduced by 18.37% and 52.47%, respectively. The concentration of free L-oxyproline under the conditions of stimulation with bacterial LPS was 7.5% higher, while the concentration of sialic acids was by 11.33% lower compared to the MetS group.

The combination of MetS and stimulation with bacterial LPS increased the total concentration of GAG by 22.53% and the heparin-heparan and keratan-dermatan fraction concentrations by 26.18 and 35.91%, respectively, but did not sta-

Table 2. Parameters of extracellular matrix degradation in the homogenate of biceps femoris muscle of rats under conditions of metabolic syndrome and stimulation with bacterial lipopolysaccharide (M ± m; n = 6)

Parameters	Groups			
	Control,	MetS	LPS	LPS + MetS
GAG concentration, μmol/l				
Total	1.82±0.02	2.500±0.005*	2.54±0.01*,**	2.230±0.004*,**,***
Heparin-heparan fraction	0.764±0.005	0.413±0.002*	1.297±0.007*,**	0.964±0.012*,**,***
Keratan-dermatan fraction	0.518±0.007	0.664±0.027*	0.542±0.012**	0.704±0.013*,***
Chonroitin fraction	0.622±0.003	1.576±0.016*	0.749±0.014*,**	0.638±0.010**,***
Concentration of free L-oxyproline, μmol/g	0.420±0.004	0.783±0.008*	0.842±0.004*,**	0.927±0.004*,**,***
Concentration of sialic acids, mg/g	6.71±0.02	11.74±0.11*	10.41±0.02*,**	17.23±0.16*,**,***

Note: *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 stimulation with bacterial lipopolysaccharide ($P < 0.05$).

tistically significantly changed the chondroitin fraction conentration compared to the control. The concentration of free L-oxyproline and sialicc acids under these conditions increased by 120.71% and 156.78%.

The combined effect of MetS and stimulation with bacterial LPS, compared to the MetS group, reduced the total concentration of GAG by 10.8%, increased the heparin-heparan fraction concentration by 2.33 times, did not have a statistically significant effect on the keratan-dermatan fraction concentration and reduced the chondroitin fraction concentration by 2.47 times. The concentrations of free L-oxyproline and sialic acids increased by 18.39 and 46.76%, respectively.

The combination of MetS and stimulation with bacterial LPS, compared to the LPS group, reduced the total concentration of GAG by 12.20%, decreased the heparin-heparan and chondroitin fraction concentrations by 1.35 and 1.17 times, respectively, and increased the keratan-dermatan fraction concentration by 29.89%. The concentration of free L-oxyproline and sialic acids increased by 10.10% and 65.51%.

A decrease in the heparin-heparan fraction of GAG concentration under conditions of MetS may be associated with increased expression of heparin-binding EGF-like growth factor (HB-EGF) [17]. HB-EGF is a transmembrane protein that is able to activate a series of redox-sensitive cascades after the addition of heparin, which leads to the development of an inflammatory reaction in muscles and contributes to the formation of insulin resistance [17]. An increase in this fraction concentration in the LPS group can be explained by the systemic effect of inflammatory mediators, since heparan sulfate is a marker of systemic inflammatory reactions [18]. However, the physiological significance of such an increase in heparin-heparan fraction of GAG under the conditions of stimulation of the organism with bacterial LPS remains debatable. On the one hand, heparan sulfate can help reduce the intensity of inflammatory reactions [19]. On the other hand, the binding of heparin, which is a part of this fraction, to the heparin-binding protein, the expression of which increases during systemic inflammatory reactions, leads to an increase in inflammatory reactions [20].

An increase in the chondroitin fraction of GAG concentration under the conditions of MetS may be an adaptive response to lipid metabolism disorders, since this fraction of GAG can influence lipid metabolism [21]. This is especially relevant in the conditions of our experimental model, which involves the use of a high-calorie diet [11]. The growth of this fraction of GAG under the conditions of stimulation of the body with bacterial lipopolysaccharide can be explained by the effect of LPS on tissue macrophages, which is also accompanied by lipid metabolism disorders due to the formation of "aging macrophages" that are able to accumulate lipid metabolism products [22].

As already mentioned above, the increase in the breakdown of collagen fibers in muscles can be associated with the transcription factor NF-κB activation and the subsequent increase in the expression of MMPs controlled by this factor [7]. Another possible cause of increased L-oxyproline concentration in animals of the LPS and combined MetS and LPS groups is development of oxidative stress caused by LPS administration [23]. The highest concentration of free L-oxyproline in the combined group may indicate a synergistic effect of both of these pathogenic influences on the activation of NF-κB-controlled MMPs.

The sialic acids content increasing in the MetS group may be a consequence of excessive activation of neuraminidase-1 [24]. Bacterial lipopolysaccharides can also activate this enzyme, which explains the sialic acids concentration increase in the LPS group [25]. A synergistic effect of the combination of MetS and stimulation with LPS on the concentration of sialic acids can be explained by different mechanisms of neuraminidase-1 activation that do not compete with each other. Under the conditions of MetS, neuraminidase-1 activation occurs through adipokines, while when exposed to LPS, neuraminidase-1 activation occurs through TLRs [24, 25].

CONCLUSIONS

1. Metabolic syndrome, stimulation of the organism with bacterial lipopolysaccharide and their combination lead to increased degradation of glycoproteins and proteoglycans and intensify collagenolysis in rat biceps femoris muscle.

2. The combination of metabolic syndrome and stimulation of the organism with bacterial lipopolysaccharide shows a synergistic effect regarding the intensity of collagenolysis and desialinization in the extracellular matrix of rat biceps femoris muscle.

3. Stimulation of the organism with bacterial lipopolysaccharide against the background of metabolic syndrome modeling limits the lipopolysaccharide-induced increase in the concentration of heparin-heparan fraction and metabolic syndrome-induced increase in the concentration of chondroitin fraction of glycosaminoglycans.

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ВПЛИВ БАКТЕРІАЛЬНОГО ЛІПОПОЛІСАХАРИДУ НА ДЕГРАДАЦІЮ КОМПОНЕНТІВ ПОЗАКЛІТИННОГО МАТРИКСУ ДВОГОЛОВОГО М'ЯЗА СТЕГНА ЩУРА ЗА УМОВ МЕТАБОЛІЧНОГО СИНДРОМУ, ІНДУКОВАНОГО ДІЄТОЮ З ВИСОКИМ ВМІСТОМ ФРУКТОЗИ

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Метаболічний синдром є епідемією неінфекційного генезу, що пов'язана із вживанням великої кількості висококалорійної їжі та малорухливим способом життя. Не виключеним є потрапляння до організму бактеріальних ліпополісахаридів (ЛПС) підчас метаболічного синдрому. Мета нашої роботи – вивчити сумісний вплив бактеріального ліпополісахариду та дієти з високим вмістом фруктози на концентрацію глікозаміногліканів та їх окремих фракцій, а також вміст вільного L-оксипроліну та сіалових кислот у двоголовому м'язі стегна щурів. Бактеріальний ЛПС вводили внутрішньоочеревинно в дозі 0,4 мкг/кг. Метаболічний синдром був змодельований з використанням 20%-го розчину фруктози як єдиного джерела питної води. У дослідній групі тварин зросла загальна концентрація глікозаміногліканів на 22,53%, концентрація гепарин-гепаранової та кератандерматанової фракції – на 26,18 та 35,91%, проте концентрація хондроїтинової фракції не змінилася порівняно з контрольною групою тварин. Концентрації вільного L-оксипроліну та сіалових кислот зросли на 120,71 та 156,78% відповідно. Таким чином, дієта з високим вмістом фруктози, стимуляція організму бактеріальним ліпополісахаридом та їх поєднання призводять до посилення деградації глікопротеїнів і протеогліканів та інтенсифікують колагеноліз у двоголовому м'язі стегна щурів.

Ключові слова: метаболічний синдром; бактеріальний ліпополісахарид; L-оксипролін; глікозаміноглікани; сіалові кислоти; двоголовий м'яз стегна.

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