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THE INFLUENCE OF STIMULATION OF ORGANISM WITH BACTERIAL LIPOPOLYSACCHARIDE ON THE BACKGROUND OF METABOLIC SYNDROME MODELING ON THE DEVELOPMENT OF OXIDATIVE STRESS IN RAT HEART

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Metabolic syndrome is one of the most widespread non-infectious pathologies in the world affecting almost a quarter of world population. The purpose of this work is to determine the activity of antioxidant enzymes, the production of superoxide anion radical, the content of oxidatively modified proteins and the concentration of malondialdehyde in the heart of rats under conditions of experimental metabolic syndrome and stimulation of the organism with bacterial lipopolysaccharide. In the test group of animals superoxide production increased by 6.31 times, activity of superoxide dismutase decreased by 2.97 times, the activity of catalase decreased by 2.4 times, the concentration of malondialdehyde increased by 3.08 times, and the content of oxidatively modified proteins increased by 2.81 times. Stimulation of organism with bacterial lipopolysaccharide on the background of induction of metabolic syndrome by high fructose diet shows synergetic effect on increase of reactive oxygen species production, severely decreases activity of antioxidant enzymes and intensifies oxidative damage to protein and lipid structures of rat heart.

Key words: metabolic syndrome, heart, rats, bacterial lipopolysaccharide, oxidative stress

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ВПЛИВ СТИМУЛЯЦІЇ ОРГАНІЗМУ БАКТЕРІАЛЬНИМ ЛІПОПОЛІСАХАРИДОМ ЗА УМОВ МОДЕЛЮВАННЯ МЕТАБОЛІЧНОГО СИНДРОМУ НА РОЗВИТОК ОКСИДАТИВНОГО СТРЕСУ У СЕРЦІ ЩУРІВ

Метаболічний синдром є однією з найпоширеніших неінфекційних патологій у світі, яка вражає майже чверть населення планети. Метою роботи є визначення активності антиоксидантних ферментів, продукції супероксидного аніон-радикала, вмісту окислювально модифікованих білків та концентрації малонового діальдегіду в серці щурів за умов експериментального метаболічного синдрому та стимуляції організму бактеріальною ліпополісахариду. У дослідній групі тварин продукція супероксиду зросла в 6,31 рази, активність супероксиддисмутази знизилася в 2,97 рази, активність каталази знизилася в 2,4 рази, концентрація малонового діальдегіду збільшилася в 3,08 рази, а вміст окислювально модифікованих білків збільшився в 2,81 рази. Стимуляція організму бактеріальним ліпополісахаридом на тлі індукції метаболічного синдрому дієтою з високим вмістом фруктози виявляє синергетичну дію на підвищення продукції активних форм кисню, різко знижує активність антиоксидантних ферментів та посилює окисне пошкодження білкових і ліпідних структур серця щурів.

Ключові слова: метаболічний синдром, серце, щури, бактеріальний ліпополісахарид, оксидативний стрес

This work is a fragment of the research project "The role of transcription factors, the circadian oscillator system and metabolic disorders in the formation and functioning of pathological systems", state registration No. 0119U103898.

Metabolic syndrome (MetS) is considered a non-infectious pandemic, that affected humanity in modern age. MetS affects almost 1/3 of population in USA. Similar prevalence is observed in highly developed countries of Europe (Great Britain, France, Germany, etc.) [2]. Following this trend MetS will soon affect more than a quarter of world population. Development of MetS is often associated with the intake of high-calorie food along with a substantial decrease in manual labor and adoption of sedentary lifestyles, sometimes such behavior is called "western life-style" [1].

MetS is often aggravated by inflammation in adipose tissue, which than transcends to systemic inflammation and can even lead to neuroinflammation [14]. Systemic inflammation during MetS is closely connected to insulin resistance development, which is one of the key features of MetS. For instance, Nicoară D.M. et al. assessed the relationship between Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and systemic immune-inflammation index (SII), and found, that both are positively associated [12]. Development of systemic inflammation during MetS leads to increased concentration of pro-inflammatory cytokines in blood (IL-1, TNF-α, IFN-γ, etc.), which in turn can lead to damage in various tissues and organs due to activation of pro-inflammatory transcriptional factors, such as NF-κB, with subsequent development of oxidative stress.

MetS represents a cluster of cardiovascular risk factors, including high blood pressure, insulin resistance, dislipidemia, and obesity that are associated with an increased risk of heart failure [4]. One of the key elements of cardiac damage caused by MetS is mitochondrial disfunction in result of insulin resistance. The main reason for mitochondrial disfunction in heart during MetS-induced insulin resistance is decreased glucose intake through GLUT-4, which causes accumulation of fatty acids, which in turn activates expression of peroxisome proliferator activator receptor alpha (PPAR-α) [4]. Excessive activation of PPAR-α during MetS can cause cardiotoxicity be increase in reactive oxygen species (ROS) formation in mitochondria with subsequent involvement of redox-sensitive transcriptional factors (NF-κB, Nrf-2, STAT-3, etc.) [5].

Bacterial infection during MetS is not excluded. Taking into account altered state of immune system during MetS bacterial lipopolysaccharides (LPS) can either be eliminated faster or cause additional increase in pro-inflammatory cytokine production, thus elevating damage to internal organs through immune mechanisms. Scientific literature provides limited and controversial data regarding influence of LPS stimulation of organism on metabolic changes in heart during MetS.

The purpose of the study was to determine the activity of antioxidant enzymes, the production of superoxide anion radical, the content of oxidatively modified proteins and the concentration of malondialdehyde in the heart of rats under conditions of experimental metabolic syndrome and stimulation of the organism with bacterial lipopolysaccharide.

Materials and methods. The study was conducted on 24 mature male Wistar rats weighing 200–260 g. The animals were randomly divided into 4 groups of 6 animals each. The first group was a control group, the animals of this group received manipulations similar to those of the other groups, but instead of the active substances, they received a 0.9 % solution of sodium chloride. The second group was the experimental metabolic syndrome group (MetS group). MetS was reproduced by using a 20 % fructose solution as the only source of water for 60 days [9]. The third group is the group of stimulation of the organism with the bacterial lipopolysaccharide (LPS) of *S. typhi* (LPS group). Stimulation of the organism with LPS was carried out 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) [10]. The fourth group is the group of the combined effect of stimulation of the organism with LPS and reproduction of MetS (LPS+MetS group). Animals of this group received a 20 % fructose solution as the only source of water and were administered LPS according to the scheme of group 3. Experiment lasted for 60 days.

The animals were kept in the vivarium of the Poltava State Medical University under standard conditions. When working with animals, the "European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes" was upheld. The withdrawal of animals from the experiment was carried out under thiopental anesthesia by taking blood from the right ventricle of the heart. All manipulations with laboratory animals were approved by Bioethical Committee of Poltava State Medical University (Record № 206 from 24.06.2022).

The object of the study was a 10 % homogenate of the heart of rats. In 10 % homogenates, basic superoxide anion radical (SAR) production, SAR production from microsomal electron transport chain (ETC), SAR production from mitochondrial ETC were studied using reduced nitroblue tetrazolium as an indicator of SAR formation [11]. The activity of superoxide dismutase (SOD, EC 1.15.1.1) was determined by the rate of inhibition of autoxidation of adrenaline in the presence of the sample. Catalase activity (EC 1.11.1.6) was determined by the rate of splitting of hydrogen peroxide in the presence of the sample [11]. The concentration of free malondialdehyde (MDA) was determined by the formation of a colored reaction product between MDA and 1-methyl-2-phenylindole [11]. The concentration of oxidatively modified proteins (OMP) was determined by determining carbonyl groups, which are formed during the interaction of reactive oxygen species with amino acid residues using 2,4-dinitrophenylhydrazine [11].

The 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 of the study and discussion. MetS modelling increased the basic production of SAR in the heart of rats by 73.02 % compared to the control group of animals (Table 1). SAR production in the heart of rats from mitochondrial ETC in the MetS group increased by 29.31 %, and from microsomal by 20.34 % compared to the control group of animals. SOD activity in the heart of rats in the MetS group decreased by 30.09 %, and catalase by 29.31 % compared to the control group of animals. The concentration of MDA in the heart of rats in the MetS group increased by 2.04 times, and the content of OMP increased by 1.65 times compared to the control group of animals.

Table 1

Parameters of the pro- and antioxidant balance in the heart of rats under the condition of modeling the metabolic syndrome and stimulation of the body with bacterial lipopolysaccharide (M±m)

Parameters	Groups			
	Control, n=6	MetS, n=6	LPS, n=6	LPS+MetS, n=6
SAR production, nmol/s per g				
Basic	0.48±0.03	1.93±0.07*	2.65±0.14 */#	3.03±0.02 */#
From microsomal ETC	10.57±0.14	12.72±0.36*	14.41±0.46 */#	15.65±0.45 */#
From mitochondrial ETC	12.11±0.18	15.66±0.06*	12.92±0.08*/#	16.66±0.89 */^
SOD activity, c.u.	8.28±0.44	5.54±0.37*	10.97±0.47*/#	2.79±0.15 */#/^
Catalase activity, μkatal/g	0.84±0.01	0.577±0.001*	0.95±0.01*/#	0.35±0.01 */#/^
Free MDA concentration, μmol/g	9.67±0.21	19.77±0.22*	21.76±1.10*	29.78±0.60 */#/^
OMP content, c.u.	0.085±0.001	0.140±0.011*	0.169±0.011*	0.239±0.002 */#/^

Note: * – data is statistically significantly different from control group ($p<0.05$). # – data is statistically significantly different from MetS group ($p<0.05$). ^ – data is statistically significantly different from LPS group ($p<0.05$).

In LPS group basic production of SAR increased in the heart of rats by 5.52 times compared to the control group. SAR production from mitochondrial ETC in the heart of rats in the LPS group of animals increased by 6.69 %, and from microsomal ETC by 36.33 % compared to the control group of animals. SOD activity in the heart of rats in the LPS group increased by 32.49 %, catalase activity increased by 13.0 % compared to the control group of animals. The concentration of MDA in the heart of rats in the LPS group increased by 2.25 times, and the content of OMP increased by 1.99 times compared to the control group. Basic production of SAR in the heart of rats in LPS group increased by 37.31 %, from microsomal ETC by 13.29 %, from mitochondrial ECT SAR production decreased by 17.5 % compared to the MetS group. SOD activity in the heart of rats in LPS group increased by 98.01 %, catalase activity by 1.65 times compared to the MetS group. There were no statistically significant changes in MDA and OMP concentration in the heart of rats between LPS and MetS groups.

Stimulation of the organism with LPS against the background of MetS modelling led to an increase in the basic production of SAR in the heart of rats by 6.31 times when compared with the control group of animals. SAR production from microsomal ETC in the heart of rats in LPS+MetS group increased by 48.06 %, from mitochondrial ETC by 37.57 % compared to the control group of animals. The activity of SOD in the heart of rats in LPS+MetS group decreased by 2.97 times, the activity of catalase decreased by 2.4 times compared to the control group of animals. The concentration of MDA in the heart of rats in LPS+MetS group increased by 3.08 times, and the content of OMP increased by 2.81 times compared to the control group of animals.

In LPS+MetS group basic production of SAR in the heart of rats increased by 1.57 times, SAR production from microsomal ETC increased by 23.03 % compared to the MetS group. The activity of SOD in the heart of rats in LPS+MetS group decreased by 1.99 times and the activity of catalase by 1.65 times compared to the MetS group. The concentration of MDA in the heart of rats in LPS+MetS group increased by 50.63 %, and the content of OMP increased by 70.71 % compared to the MetS group.

The basic production of SAR in the heart of rats in LPS+MetS group and the production of SAR from microsomal ETC did not change significantly, but SAR production from mitochondrial ETC increased by 28.94 % compared to the LPS group. The activity of SOD in the heart of rats in LPS+MetS group decreased by 3.93 times and catalase activity decreased by 2.71 times compared to the LPS group. The concentration of MDA in the heart of rats in the LPS+MetS group increased by 36.86 %, and the OMP content increased by 41.42 % compared to the LPS group.

All studies pathogenic factors (stimulation of organism with bacterial LPS, induction of metabolic syndrome by high fructose diet and their combination) lead to development of oxidative stress in heart of rats. However, oxidative stress has peculiarities in each studied group. In MetS group oxidative stress is the result of increase reactive oxygen species (ROS) formation on the background of decreased activities of studied antioxidant enzymes. In LPS group situation is different increased ROS formation is accompanied with elevated activities of antioxidant enzymes. However, increased activity of antioxidant enzymes clearly cannot compensate the greater (compared to MetS group) ROS formation and situation still results in oxidative stress development. In LPS+MetS group we can observe, that increase in SAR production from microsomal ETC is based on LPS stimulation, while increase in SAR production from mitochondrial ETC is mostly based on MetS modelling. Combination of MetS modelling and LPS stimulation shows clear synergetic effect on increase of intensity of lipid peroxidation and oxidative damage to proteins. In LPS+MetS group we can also observe an exhaustion of antioxidant enzymes on the background of the highest ROS production from the studied groups.

Stimulation of ROS production from mitochondrial ETC in MetS group can be explained by already mentioned decrease in glucose uptake by mitochondria due to lower influx of glucose through

GLUT-4 during insulin resistance caused by MetS, and subsequent increased PPAR-α activation [4, 5]. More profound effect of LPS on ROS production from microsomal ETC can be explained by increased activation of Toll-like receptors (TLR) by bacterial LPS used in our study, which leads to increased expression of inducible NO-synthase and endothelial NO-synthase uncoupling, due to NF-κB activation [13]. Excessive activation of NF-κB through TLR can explain increased SOD activity in LPS group, and increased SOD activity creates an opportunity for substrate induction of catalase, since main product formed in SOD-controlled SAR degradation is hydrogen peroxide.

Decreased activity of SOD during high fructose diet-induced MetS can be associated with development of insulin resistance. Liu Y. et al. showed in their study that decrease in SOD activity during MetS is connected to glucose levels and insulin sensitivity [8]. Decreased SOD activity in MetS group naturally leads to lower amount of hydrogen peroxide formed in SOD-dependent SAR degradation and lowers substrate induction of catalase, hence we observed decreased activity of these enzymes in MetS group.

Li J. et al. stress on importance of mitochondrial dysfunction and mitochondria-produced ROS in formation of cardiomyopathy [6]. One of the main mechanisms of impaired mitochondrial function during MetS according to Li J. et al. is a decrease in NAD+/NADH coupling caused by excessive influx of fatty acids [6]. Our results also show increased ROS production from mitochondrial ETC both in MetS group and LPS+MetS group. This suggests impairment of mitochondria in both studied groups. LPS can also influence mitochondria and cause increased ROS generation from its ETC. However, such ROS generation is caused through inflammasome formation and activation [3].

As we have mentioned before LPS can cause endothelial NO-synthase uncoupling and increase ROS formation from microsomal ETC [13]. MetS can also lead to endothelial NO-synthase uncoupling and increased ROS production from microsomal ETC [7]. Therefore, MetS and LPS have similar mechanisms which can lead to increased ROS formation. This can explain the synergetic effect caused by combination of LPS stimulation of organism with high fructose diet on ROS generation. Taking into account that catalase is a rate limiting enzyme in SOD-catalase system we can assume, that decrease in activities of these enzymes in LPS+MetS group is caused by inability of catalase to process the excess of hydrogen peroxide formed from SOD-controlled SAR degradation and from other sources, which may subsequently lead to damage to SOD protein structure.

Conclusion

Stimulation of organism with bacterial lipopolysaccharide, induction of metabolic syndrome by high fructose diet and their combination lead to increased formation of reactive oxygen species, disturb antioxidant protection, intensify lipid peroxidation and protein oxidation in rat heart.

Stimulation of organism with bacterial lipopolysaccharide on the background of induction of metabolic syndrome by high fructose diet shows synergetic effect on increase of reactive oxygen species production, severely decreases activity of antioxidant enzymes and intensifies oxidative damage to protein and lipid structures of rat heart.

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OXIDATIVE STRESS IN LIVER TISSUES AT ALCOHOLIC HEPATITIS AND ITS CORRECTION BY A COMPLEX COMPOUND SYNTHESIZED ON THE BASIS OF PALLADIUM AND MEXIDOL

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An experiment was conducted on 20 white rats bred in vivarium conditions at the Research Center of the Azerbaijan Medical University, and divided into 4 groups. The 1st group included intact experimental animals, the 2nd-4th groups – experimental animals simulating alcoholic hepatitis. A complex compound (mexidazole) synthesized on the basis of palladium and mexidol was injected into the abdominal cavity of group 3 animals for 3 days, and group 4 animals – for 7 days at a dose of 0.02 mg/kg. A model of alcoholic hepatitis has been developed. In the homogenate, the average concentrations of surface-located SH-groups, internal protein-SH-groups, peroxidase, catalase and total antioxidant activity decreased compared to the intact state. In the blood of experimental animals, due to the action of alcohol, the activity of liver enzymes significantly increased, free lipid peroxidation increased in the liver tissue. The body's antioxidant defense system has significantly weakened. The results of the 3rd group of experimental animals showed that oxidative stress in the liver continues even after 10 days since the creation of the alcoholic hepatitis model. After injection of 0.02 mg/kg of mexidozole into the abdominal cavity for 3 days, the concentration of these enzymes in the blood tended to decrease. After daily administration of mexidozole at a dose of 0.02 mg/kg for 3 days into the abdominal cavity of white rats against the background of an alcoholic hepatitis model, pronounced positive changes in the dynamics of oxidative stress were noted.

Key words: alcohol, hepatitis, enzymes, oxidative stress, palladium and mexidol.

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ОКИСЛЮВАЛЬНИЙ СТРЕС У ТКАНИНАХ ПЕЧІНКИ ПРИ АЛКОГОЛЬНОМУ ГЕПАТИТІ ТА ЙОГО КОРЕКЦІЯ КОМПЛЕКСНОЮ СПОЛУКОЮ, СИНТЕЗОВАНОЮ НА ОСНОВІ ПАЛАДІЮ І МЕКСИДОЛУ

Було проведено експеримент на 20 білих щурах, розділених на 4 групи. До 1-ї групи увійшли інтактні експериментальні тварини, до 2–4-ї груп – експериментальні тварини, у яких моделювали алкогольний гепатит. Комплексну сполуку (мексидазол), синтезовану на основі паладію та мексидолу, вводили в черевну порожнину тваринам 3-ї групи протягом 3-х діб, а тваринам 4-ї групи – протягом 7 діб у дозі 0,02 мг/кг. Розроблено модель алкогольного гепатиту. У гомогенаті середні значення концентрації поверхнево-розташованих SH-груп, внутрішніх білково-SH-груп, пероксидази, каталази та загальної антиоксидантної активності порівняно з інтактним станом зменшилися. У крові піддослідних тварин за рахунок дії алкоголю значно збільшились показники активності печінкових ферментів, у тканинах печінки посилювалося вільне перекисне окиснення ліпідів. Система антиоксидантного захисту організму значно послабшала. Результати 3-ї групи піддослідних тварин показали, що окислювальний стрес у печінці триває навіть через 10 днів з моменту створення моделі алкогольного гепатиту. Після введення в черевну порожнину 0,02 мг/кг мексидозолу протягом 3 днів концентрація цих ферментів у крові мала тенденцію до зниження. Після щоденного введення мексидозолу в дозі 0,02 мг/кг протягом 3 днів у черевну порожнину білих щурів на фоні моделі алкогольного гепатиту відмічені виражені позитивні зміни в динаміці оксидативного стресу.

Ключові слова: алкоголь, гепатит, ферменти, окислювальний стрес, паладій та мексидол.

Alcohol is the main cause of liver damage and contributes significantly to the genesis of overall morbidity and mortality. Today, alcohol consumption is especially common among the general population. The problem of alcoholic liver damage still does not lose its relevance. Today, alcohol consumption is especially common among the general population. The study of its negative impact on human health and the organization of its rehabilitation is one of the priority tasks facing medicine. The