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Influence of organism stimulation with bacterial lipopolysaccharide on nitric oxide production and metabolism in rat heart on the background of metabolic syndrome

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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Aim. The aim of the study was to establish the changes in nitric oxide production and metabolism in rat heart during combined influence of organism stimulation with bacterial lipopolysaccharide (LPS) and modeling of metabolic syndrome (MetS).

Materials and methods. The study was conducted on 24 mature male Wistar rats weighing 200–260 g. Experiment lasted 60 days. The animals were divided into 4 groups of 6 animals each: control group, MetS group, LPS stimulation group, LPS + MetS group. MetS was reproduced by using a 20 % fructose solution as the only source of drinking water. LPS of *Salmonella typhi* was administered at a dose of 0.4 μg/kg intraperitoneally. Animals from LPS + MetS group received a 20 % fructose solution as the only source of drinking water and were administered LPS. In 10 % tissue homogenate of rat heart we studied: total activity of NO-synthases (NOS), activity of constitutive (cNOS) and inducible (iNOS) isoforms, activity of nitrate (NaR) and nitrite (NiR) reductases, concentration of peroxynitrites ($ONOO^-$), nitrites, nitrosothiols and hydrogen sulfide.

Results. Combination of MetS and stimulation of organism with LPS led to increase in total NOS activity by 32.72 % compared to control group. Activity of cNOS did not change compared to control group. Activity of iNOS increased by 33.76 %. Arginase activity decreased by 23.53 %. NaR activity and NiR activity were increased by 86.67 % and by 149.29 %, respectively. Combination of MetS and stimulation of organism with LPS led to decrease in nitrite and nitrosothiols concentration by 38.73 % and by 54.79 %, respectively. Under these conditions concentration of $ONOO^-$ elevated by 398.0 % compared to control group. Concentration of H_2S decreased by 27.56 %.

Conclusions. Combination of metabolic syndrome and stimulation of organism with bacterial lipopolysaccharide leads to prevalence of peroxynitrite formation during increased nitric oxide production NO-synthase-dependent and nitrate-nitrite-NO pathways in rat heart.

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Вплив стимуляції організму бактеріальним ліпополісахаридом на продукцію та метаболізм оксиду азоту в серці щурів за умов метаболічного синдрому

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Мета роботи – встановлення змін продукції та метаболізму оксиду азоту в серці щурів під час комбінованого впливу на організм стимуляції бактеріальним ліпополісахаридом (ЛПС) та моделювання метаболічного синдрому (МетС).

Матеріали та методи. Дослідження здійснили на 24 статевозрілих самцях щурів лінії Вістар масою 200–260 г. Експеримент тривав 60 днів. Тварин поділили на 4 групи по 6 особин: контрольна група, група МетС, група стимуляції ЛПС, група ЛПС + МетС. МетС відтворений із використанням 20 % розчину фруктози як єдиного джерела питної води. ЛПС *Salmonella typhi* вводили інтроперитонеально в дозі 0,4 мкг/кг. Тварини з групи ЛПС + МетС отримували 20 % розчин фруктози як єдине джерело питної води, а також їм вводили ЛПС. У 10 % тканинному гомогенаті серця щурів досліджували сумарну активність NO-синтаз (NOS), активність конститутивної (cNOS) та індуцибельної (iNOS) ізоформ, активність нітрат (NaR) і нітрит (NiR) редуктаз, концентрацію пероксинітритів ($ONOO^-$), нітритів, нітрозотіолів і гідроген сульфіду.

Результати. Поєднання МетС і стимуляції організму ЛПС призвело до збільшення сумарної активності NOS на 32,72 % порівняно з контрольною групою. Активність cNOS порівняно з контрольною групою не змінилась. Активність iNOS зросла на 33,76 %. Активність аргінази знизилася на 23,53 %. Активність NaR і NiR зросла на 86,67 % та 149,29 % відповідно. Поєднання МетС і стимуляції організму ЛПС спричинило зниження концентрації нітритів і нітрозотіолів на 38,73 % і 54,79 % відповідно. За цих умов концентрація $ONOO^-$ підвищилася на 398,0 % порівняно з контрольною групою. Концентрація H_2S зменшилася на 27,56 %.

Висновки. Поєднання метаболічного синдрому та стимуляції організму бактеріальним ліпополісахаридом призводить до переважання утворення пероксинітриту під час підвищеного утворення оксиду азоту від NO-синтазозалежного та нітрат-нітрит-NO шляхів у серці щурів.

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Nitric oxide (NO) is an important regulator of vascular tonus, as well as a signal molecule. Its function in heart is rather well established [1]. However, besides signaling and vascular tonus control functions NO can affect redox homeostasis and lead to development of oxidative and nitrosative damage to cells and tissues [2,3]. In mammalian cells NO is predominantly produced by specific enzymes, namely, nitric oxide synthases (EC 1.14.13.39, NOS). NOS can produce nitric oxide by transformation of L-arginine to L-citrulline in presence of electron donor (NADPH + H) and oxygen.

In the case of hypoxia or lack of substrate for NOS function another pathway of nitric oxide production exists. Nitric oxide can be formed from nitrates and nitrites by their enzymatic and non-enzymatic reduction [4]. Enzymes responsible for reduction of nitrates and nitrites to nitric oxide work in tandem and are called nitrate (NaR) and nitrite (NiR) reductases. They act like a backup system to ensure sufficient production of nitric oxide even under hypoxic conditions or other cases of NOS-dependent NO production impairment. This reductive pathway of NO synthesis is used for treatment of heart failure for many years [5].

Metabolic syndrome (MetS) is well known for its ability to cause heart failure and other cardiac diseases [6]. One of the mechanisms underlying cardiac complications of MetS is disruption of NO synthesis and utilization [7,8]. On the other hand, bacterial lipopolysaccharide (LPS), which can enter blood during sepsis may also lead to impaired NO synthesis, and endothelial dysfunction [9]. Taking into account, that patients with MetS are more prone to bacterial invasions, simultaneous influence of LPS and MetS on organism cannot be excluded [10]. Scientific literature provides limited amount of data about combined effect of LPS and MetS on production and utilization of NO in heart.

Aim

The aim of the study was to establish the changes in nitric oxide production and metabolism in rat heart during combined influence of organism stimulation with bacterial lipopolysaccharide and modeling of metabolic syndrome.

Materials and methods

The study was conducted on 24 mature male Wistar rats weighing 200–260 g. The animals were divided into 4 groups of 6 animals each: control group, MetS group, LPS stimulation group, LPS + MetS group. MetS was reproduced by using a 20 % fructose solution as the only source of drinking water for 60 days [11]. Stimulation of the organism with the bacterial LPS of *Salmonella typhi* (*S. typhi*) was carried out according to the following scheme: in the first week, 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]. Animals from LPS + MetS group received a 20 % fructose solution as the only source of drinking water and were administered LPS according to the scheme of LPS stimulation group.

The animals were kept in the vivarium of the Poltava State Medical University under standard conditions. We worked with laboratory animals according to "European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes". 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 the Bioethics Commission of the Poltava State Medical University (Record No. 206 from 24.06.2022).

The object of the study was a 10 % homogenate of rat heart. Tissue homogenate was prepared on Tris-HCl buffer solution (0.2 M, pH = 7.4) by homogenization of 1 g of tissue in 9 ml of Tris-HCl buffer. Total NOS activity was evaluated by increase in nitrite (NO_2^-) concentration after incubation homogenated tissue samples for 30 min at temperature 37 °C in the incubation solution (3.1 ml) containing: 2.5 ml of 161 mM Tris-buffer (pH = 7.4), 0.3 ml of 31 mM L-arginine, 0.1 ml 32 μM NADPH and 0.2 ml of 10 % tissue homogenate [13].

In order to evaluate the activity of constitutive isoforms of NO-synthase (cNOS) we used following procedure: 0.2 ml of 10 % tissue homogenate was taken for analysis and was incubated for 60 min at t = 37 °C in incubation solution (3.3 ml) containing: 2.5 ml of 152 mM Tris-buffer (pH = 7.4), 0.3 ml of 29 mM L-arginine, 0.2 ml of 545 μM aminoguanidine hydrochloride and 0.1 ml of 30 μM NADPH. Activity of inducible isoform of NO-synthase (iNOS) was calculated by formula: iNOS = NOS-cNOS (μmol/min per g of protein) [12,13]. We used Griess–Ilosvay reagent for nitrite estimation (1 % sulfanilic acid in 30 % acetic acid and 0.1 % 1-naphtylamine in the same solvent) [12].

Total activity of arginases was assessed by difference of L-ornithine concentration before and after incubation of 0.1 ml of 10 % tissue homogenate in incubation solution (0.8 ml) containing 0.5 ml of 125 mM phosphate buffer (pH = 7.0), 0.2 ml of 6 mM L-arginine [13]. Evaluation of L-ornithine was performed after addition 0.1 ml of modified Chinard's reactive (2.5 % ninhydrin on acidic mixture consisting from 2:3 60 % orthophosphoric and ice acetic acids mixed at ratio 6:4 with water) and 1.0 ml of ice acetic acid [12].

Nitrite reductase (NiR) activity was assessed by decrease in nitrite content after 60 min at t = 37 °C incubation of 0.2 ml of 10 % tissue homogenate in incubation medium (2.3 ml) consisting of: 1 ml of 87 mM phosphate buffer (pH = 7.0), 1 ml of 4.35 mM sodium nitrite, and 0.1 ml of 61 μM NADH. Nitrites content was measured before and after incubation [12,13].

Nitrate reductase (NaR) activity was assessed by decrease in nitrate content after 60 min at t = 37 °C incubation of 0.2 ml of

Table 1. Production and metabolism of nitric oxide in rat heart under conditions of metabolic syndrome and stimulation of the organism with bacterial lipopolysaccharide (M ± SE)

Parameter, units of measurement		Groups			
		Control, n = 6	MetS, n = 6	LPS stimulation, n = 6	LPS + MetS, n = 6
NOS activity, μmol/min per g of protein	Total	1.62 ± 0.02	2.38 ± 0.03*	2.30 ± 0.02*	2.15 ± 0.02*,#,^
	cNOS	0.0530 ± 0.0002	0.0470 ± 0.0003*	0.0930 ± 0.0008*,#	0.0530 ± 0.0003#,^
	iNOS	1.57 ± 0.02	2.34 ± 0.03*	2.21 ± 0.02*,#	2.10 ± 0.02*,#,^
Arginase activity, μmol/min per g of protein		2.21 ± 0.03	2.87 ± 0.02*	0.77 ± 0.02 *,#	1.69 ± 0.03*,#,^
Nitrate reductase activity, μmol/min per g of protein		5.27 ± 0.28	6.74 ± 0.67*	5.18 ± 0.17#	9.89 ± 0.33*,#,^
Nitrite reductase activity, μmol/min per g of protein		4.24 ± 0.18	10.85 ± 0.35*	13.47 ± 0.54*,#	10.57 ± 0.10*,^
Nitrite concentration, nmol/l		7.85 ± 0.12	3.14 ± 0.27*	11.10 ± 0.23*,#	4.81 ± 0.18*,#,^
$ONOO^-$ concentration, μmol/g		0.50 ± 0.03	2.10 ± 0.05*	0.53 ± 0.02#	2.49 ± 0.03*,#,^
Concentration of nitrosothiols, μmol/g		0.73 ± 0.03	0.57 ± 0.03*	1.15 ± 0.03*,#	0.33 ± 0.03*,#,^
Concentration of H_2S, μmol/g		10.34 ± 0.21	12.05 ± 0.37*	5.23 ± 0.37*,#	7.49 ± 0.18*,#,^

***:** significant difference compared to control group ($p < 0.05$); **#:** significant difference compared to experimental metabolic syndrome group ($p < 0.05$); **^:** significant difference compared to the group of the organism stimulation by bacterial lipopolysaccharide ($p < 0.05$).

10 % tissue homogenate in incubation medium (2.3 ml) consisting of: 1 ml of 87 mM phosphate buffer (pH = 7.0), 1 ml of 4.35 mM sodium nitrate, and 0.1 ml of 61 μM NADH [12,13].

Concentration of peroxynitrites of alkali (Na^+, K^+) and alkali-earth (Ca^{2+}) metals was measured by using its reaction with potassium iodide under pH = 7.0 in 0.2 M phosphate buffer with the same pH [13]. Concentration of low molecular weight S-nitrosothiols (S-NO) was determined by increase in nitrite concentration after 30 min incubation of 0.2 ml of 10 % tissue homogenate in incubation solution (2.6 ml) containing: 2.0 ml of 154 mM phosphate buffer (pH = 7.0), 0.1 ml of 923 μM sodium fluoride, and 854 μM mercury chloride [13].

Concentration of H_2S was estimated by amount of a color dye formed in reaction of H_2S with specific sulfide coloring reagent (0.4 g of N,N-dimethyl-p-phenylenediamin and 0.6 g of iron (III) chloride ($FeCl_3 \cdot 6H_2O$) dissolved in 100 ml of 6 M HCl) [14].

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

Results

We established in our previous work, that addition of 20 % fructose solution as the only source of drinking water to standard ration of rats leads to development of features characteristic to metabolic syndrome [13].

Modeling of MetS led to increase in total NOS activity by 46.91 % compared to control group (*Table 1*). Activity of cNOS decreased by 11.32 % compared to control group. Activity of iNOS increased by 48.04 %. Arginase activity elevated by 29.86 %. NaR activity and NiR activity were increased by 27.89 % and by 155.90 %, respectively. MetS led to decrease in nitrite and nitrosothiols concentration by 60.00 % and by 21.92 %, respectively. Under MetS conditions concentration of $ONOO^-$ elevated by 320.0 % compared to control group. Concentration of H_2S increased by 16.54 %. Therefore, MetS leads to overproduction of NO by NOS-dependent mechanism (due to increased iNOS activity) and by nitrate-nitrite-NO pathway. Simultaneously MetS elevates intensity of highly toxic reactive nitrogen species (peroxynitrites) formation, while decreasing formation of excretory (nitrites) and deposited (nitrosothiols) forms of NO in rat heart.

Stimulation of organism with LPS led to increase in total NOS activity by 41.98 % compared to control group (*Table 1*). Activity of cNOS increased by 75.47 % compared to control group. Activity of iNOS increased by 40.76 %. Arginase activity decreased by 65.16 %. NaR activity did not changed statistically significantly. NiR activity increased by 217.69 %. Stimulation of organism with LPS led to increase in nitrite and nitrosothiols concentration by 41.40 % and by 57.53 %, respectively. Under these conditions concentration of $ONOO^-$ did not changed statistically significantly compared to control group. Concentration of H_2S decreased by 49.42 %. Therefore, stimulation of organism with LPS leads to overproduction of NO by NOS-dependent mechanism and by nitrate-nitrite-NO pathway. However, stimulation of organism with LPS does not change the intensity of highly toxic reactive nitrogen species (peroxynitrites) formation, and increases formation of excretory (nitrites) and deposited (nitrosothiols) forms of NO in rat heart.

Comparing influence of stimulation of organism with LPS with MetS we can state that total NOS activity did not change compared to MetS group (*Table 1*). Activity of cNOS increased by 97.87 % compared to MetS group. Activity of iNOS decreased by 5.56 %. Arginase activity decreased by 73.17 %. NaR activity decreased by 23.15 %. NiR activity increased by 24.15 %. Stimulation of organism with LPS led to increase in nitrite and nitrosothiols concentration by 253.50 % and by 101.75 %, respectively. Under

these conditions concentration of $ONOO^-$ decreased by 74.76 % compared to MetS group. Concentration of H_2S decreased by 56.60 % compared to MetS group.

Combination of MetS and stimulation of organism with LPS led to increase in total NOS activity by 32.72 % compared to control group (*Table 1*). Activity of cNOS did not change compared to control group. Activity of iNOS increased by 33.76 %. Arginase activity decreased by 23.53 %. NaR activity and NiR activity were increased by 86.67 % and by 149.29 %, respectively. Combination of MetS and stimulation of organism with LPS led to decrease in nitrite and nitrosothiols concentration by 38.73 % and by 54.79 %, respectively. Under these conditions concentration of $ONOO^-$ elevated by 398.0% compared to control group. Concentration of H_2S decreased by 27.56 %.

Comparing combined influence of stimulation of organism with LPS and MetS with results in MetS group we can state that total NOS activity decreased by 9.66 % compared to MetS group (*Table 1*). Activity of cNOS decreased by 12.77 % compared to MetS group. Activity of iNOS decreased by 10.26 %. Arginase activity decreased by 41.11 %. NaR activity increased by 46.74 %. NiR activity did not change. Combined influence of stimulation of organism with LPS and MetS led to increase in nitrite concentration by 53.18 %, but decreased nitrosothiols concentration by 42.11 %. Under these conditions concentration of $ONOO^-$ increased by 18.57 % compared to MetS group. Concentration of H_2S decreased by 37.84 % compared to MetS group.

Comparing combined influence of stimulation of organism with LPS and MetS with results in LPS stimulation group we can state, that total NOS activity decreased by 6.52 % compared to LPS stimulation group (*Table 1*). Activity of cNOS decreased by 43.01 % compared to LPS stimulation group. Activity of iNOS decreased by 4.98 %. Arginase activity increased by 119.48 %. NaR activity increased by 90.93 %. NiR activity decreased by 21.53 %. Combined influence of stimulation of organism with LPS and MetS led to decrease in nitrite and nitrosothiols concentration by 56.67 % and 71.30 %, respectively. Under these conditions concentration of $ONOO^-$ increased by 369.81 % compared to LPS stimulation group. Concentration of H_2S increased by 43.21 % compared to LPS stimulation group.

Discussion

MetS and stimulation of organism with bacterial LPS have opposite effects on activity of cNOS. During combination of MetS and stimulation of organism with bacterial LPS inhibitory effect of MetS is dominant. Inhibitory effect of MetS on endothelial NOS (eNOS) activity is one of characteristic features of MetS and diabetes mellitus, and this is the cause of endothelial dysfunction development during MetS [15]. Several mechanisms are involved in decrease in eNOS activity during MetS. On the one hand, we observed increase in arginase activity in MetS group, which creates possibility for involvement of "arginine steal" mechanism [16]. On the other hand, increased concentration of peroxynitrite can also lead to eNOS inhibition [17]. Besides inhibition of eNOS activity peroxynitrite can cause eNOS uncoupling, which will lead to formation of reactive oxygen species (ROS) derived from eNOS electron transport chain [18]. We established that stimulation of organism with LPS increased cNOS activity in rat heart, which is different from effect of LPS on skeletal muscle [13]. Several studies show, that during LPS-induced changes in organism transcription of eNOS and neuronal NOS (nNOS) genes are decreased [19,20]. However, there is an opinion, that this effect may depend of dosage of LPS and targeted organ, as it was shown in a study of Z. Peng et al. has showed, that LPS treatment can increase eNOS expression [21].

Opposite effects of MetS and stimulation of organism with bacterial LPS on arginase activity may be due to changes in macrophage polarization caused by LPS [22]. Therefore, predominance of pro-inflammatory macrophages in LPS stimulation group may explain decrease in arginase activity observed in this group. Despite the ability of MetS to induce change in macrophage polarization towards pro-inflammatory phenotype, these metabolically activated macrophages have different energy metabolism, which enables foam cell formation and increased arginase activity in tissue or organ [23]. The exact mechanism involved in obesity-induced arginase upregulation remains unclear but may be related to impaired secretion of adipokines [24].

MetS and stimulation of organism with bacterial LPS have a potential for induction of nitrate-nitrite-NO pathway of nitric oxide production. Reduction of nitrates to nitrites and nitrites to nitric oxide both require one electron. This process can be enzymatically controlled or non-enzymatically controlled. An example of non-enzymatically controlled reduction of nitrates to nitrites is donation of one electron derived from mitochondrial complexes [25]. A potential core enzyme responsible for enzymatically controlled reduction of nitrates to nitrites and further to nitrites to nitric oxide is xanthine oxidoreductase (EC 1.1.1.204 and EC 1.17.3.2, XOR), which consists from two main domains: xanthine oxidase (EC 1.17.3.2, XO) and xanthine dehydrogenase (EC 1.1.1.204, XD). XOR is upregulated under conditions of MetS, which explains an increase in NaR and NiR activities observed in MetS group in our experiment [26]. During LPS stimulation XOR can also be upregulated due to transition of macrophages polarization towards predominance of pro-inflammatory phenotypes [27]. And increase in NiR activity observed in LPS stimulation group may be related to adaptive reaction aimed at stabilization of mitochondrial function [28].

Another important substance which controls mitochondrial function and NO synthesis is hydrogen sulfide (H_2S) [29]. H_2S can control mitochondrial functions via interaction with NO and reactive oxygen species as well as by influencing activation of redox-sensitive transcriptional factors like NF-κB, which play crucial role in development of hyperproduction of NO during various pathological conditions [30,31,32]. Hydrogen sulfide can attenuate NF-κB activation both during MetS and stimulation of organism with bacterial LPS [33,34]. This, in turn, can decrease nitric oxide and ROS production [35,36]. Therefore, we can assume, that increase in H_2S concentration during MetS observed in our study is beneficial event aimed at controlling of NF-κB activation, while decrease in its concentration during stimulation of organism with LPS evidences about inability of this mechanism to compensate excessive stimulation of NF-κB activation.

Conclusions

1. Metabolic syndrome increases production of NO in rat heart by NO-synthase-dependent and nitrate-nitrite-NO pathways resulting in excessive peroxynitrite formation.

2. Stimulation of organism with bacterial lipopolysaccharide increases production of NO in rat heart by NO-synthase-dependent and nitrate-nitrite-NO pathways resulting in accumulation of nitrites and nitrosothiols, while omitting excessive peroxynitrite formation.

3. Combination of metabolic syndrome and stimulation of organism with bacterial lipopolysaccharide leads to prevalence of peroxynitrite formation during increased nitric oxide production NO-synthase-dependent and nitrate-nitrite-NO pathways in rat heart.

Prospects for future scientific research: a viable approach to further investigation of metabolic syndrome pathogenesis is to study influence of specific inhibitors of NF-κB cascade activation on production and metabolism of nitric oxide, development of oxidative stress and degradation of connective tissue components not only in heart, but in other organs and tissues. It is of interest to further investigate the influence of changes in hydrogen sulfide concentration on nitric oxide cycle in heart.

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