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Influence of lipopolysaccharide on the development of oxidative-nitrosative stress in the liver of rats under conditions of chronic alcohol intoxication

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Alcohol abuse is a common phenomenon among the countries of the European continent. One of the first organs suffering from alcohol-induced damage is the liver. Activation of Kupffer cells, as part of the mononuclear phagocyte system, plays a significant role in the development of oxidative-nitrosative damage of the liver. Systemic inflammatory response affects the polarization of macrophages throughout the body and may affect the development of alcohol damage of hepatocytes. The aim of this work is to study the effect of in vivo stimulation by S. typhi bacterial lipopolysaccharide on the development of oxidative-nitrosative stress in rat liver under conditions of chronic alcohol intoxication. Male Wistar rats were randomly divided into 4 groups: I - control; II - rats received 0.4 μg/kg of bacterial lipopolysaccharide of S. typhi; III - rats with induced alcoholic hepatitis, and IV - rats with chronic alcohol intoxication and injected bacterial lipopolysaccharide. The experiment lasted 63 days. We studied pro-oxidants antioxidant enzymes, the concentration of sulfide anion, nitric oxide production and malonic dialdehyde concentration in liver tissues. In vivo administration of bacterial lipopolysaccharide enhances ethanol-induced oxidative liver damage via increased production of superoxide anion despite the adaptive increase in the activity of antioxidant enzymes. Nitric oxide, the production of which increases in the liver during prolonged stimulation of the rat body with bacterial lipopolysaccharide, chronic alcohol intoxication and their combination, mainly metabolizes to peroxynitrite.

Key words: lipopolysaccharide-induced hepatitis; alcoholic hepatitis; nitric oxide cycle; sulfide anion.

INTRODUCTION

Of the three known pathways for the metabolism of ethanol in the liver, only its use by catalase as a proton donor in the conversion of hydrogen peroxide to water converts ethanol to acetaldehyde without the formation of reactive oxygen species (ROS) [1]. ROS such as superoxide anion radical, hydroxyl radical, hydrogen peroxide, etc. are able to initiate the processes of lipid peroxidation and lead to the development of oxidative stress [2].

Excessive intake of ethyl alcohol leads to increased production of nitric oxide in liver tissue [3]. This, along with the overproduction of ROS, alcohol intake can lead to the formation of peroxynitrite and the development of nitrosative stress. The main producer of nitric oxide during its ethanol-induced hyperproduction is the inducible isoform of NO synthase (iNOS) [4], which is most often expressed in tissue macrophages and is a marker of their pro-inflammatory (M1) polarization.

Alcohol consumption contributes to liver inflammation by enhancing the translocation of intestinal microbiota endotoxins into the portal circulation [5, 6] and by activating Kupffer cells through lipopolysaccharide/Toll-like receptor-4 pathways, which leads to a change in the polarization of liver macrophages towards the predominance of the M1 phenotype [7, 8]. Another possible pathway of alcohol-induced shift of polarization of liver macrophages towards M1 phenotype is development of endoplasmic reticulum stress in hepatocytes [9]. This leads to oxidative damage and necrosis of hepatocytes, which in turn releases damage

associated molecular patterns (DAMPs) in surrounding tissues. DAMPs can also activate Kupffer cells and shift liver macrophages to M1 phenotype [10]. Macrophages activated by M1 phenotype become the sources of ROS and nitric oxide, which leads to the development of alcoholic liver damage. However, according to the scientific literature, liver macrophages can be activated by extrahepatic chronic inflammatory response and they have the ability to potentiate the inflammatory response, which activated them [11, 12].

The aim of this work is to examine the effect of stimulation of organism by bacterial lipopolysaccharide on the development of oxidative-nitrosative stress in the liver of rats under conditions of chronic alcohol intoxication.

METHODS

The experiments were performed on 24 white adult male Wistar rats weighing 180-220 g. The animals were divided into 4 groups. Group I was a control (n = 6) group; group II consisted from rats (n = 6) exposed to pyrogenal (bacterial lipopolysaccharide (LPS) from *S. typhi*) administered intraperitoneally at the dose of 0.4 μg/kg in the first week 3 times a week, thereafter once a week throughout the experiment [13]; group III consisted from rats with alcoholic hepatitis (n = 6) simulated by forced intermittent alcoholisation for 5 days, with repetition after every two days, by intraperitoneal administration of 16.5% ethanol solution in 5% glucose solution, at the rate of 4 ml/kg of body weight. Afterwards they were given 10% ethanol solution as the only source of water [14]. Group IV consisted from rats (n = 6), on which we simulated chronic alcohol intoxication as in group III and injected pyrogenal according to the scheme of the group II.

The control group included rats, on which we performed similar manipulations throughout the study, but injected saline instead of specified chemical compounds. Conditions for keeping animals in the vivarium were standard. Withdrawal of animals from the experiment occurred on the day 63 by taking blood from the right ventricle of the heart under thiopental anesthesia. Serum and liver were studied. During the experiments, the recommendations of the "European Convention for the protection of vertebrate animals used for experimental and other scientific purposes" were followed (Strasbourg, 1986). We performed our research in accordance with the "General Principles of Animal Experiments" approved by the First National Congress of Bioethics, and the requirements of the "Procedure for conducting scientific experiments, experiments on animals" (2012).

The activity of iNOS and constitutive isoforms of NO synthase (cNOS) [15, 16], the activity of superoxide dismutase (SOD) [17] and catalase [18], the concentration of malonic dialdehyde (MDA) [19], peroxynitrites of alkali and alkali-earth metals ($ONOO^-$) [15], nitrites [15], low molecular weight S-nitrosothiols (S-NO) [20], sulfide anion [21] and superoxide anion production [22] were determined in the rat liver homogenate.

Statistical processing of the results of biochemical studies was performed using paired comparison by nonparametric Mann-Whitney U-test. All statistical calculations were performed in Microsoft office Excel and its extension Real Statistics 2019. The difference was considered statistically significant at $P < 0.05$.

RESULTS AND DISCUSSION

The effect of lipopolysaccharide stimulation on the biochemical parameters of rat liver. It is well known that the intestinal microbiota affects the development of liver disease through the intestinal-liver axis [23, 24]. It is also an established fact that bacterial lipopolysaccharide may lead to change liver macrophages into M1 phenotype [25]. We found that after administration of bacterial lipopolysaccharide, the activity of NO-synthases in the liver of rats statistically significantly increased, in particular, iNOS increased 1.85 times and cNOS elevated 1.44

times compared to the control group (Table). Under these conditions, the concentration of $ONOO^-$ in the liver increased 9.6 times, and the concentration of nitrites and S-NO decreased by 1.85 times and 1.71 times, respectively compared to the control group. Thus, lipopolysaccharide activated the development of nitrosative stress in the liver of rats, which coincides with the research of other scientists [26, 27].

By analyzing antiradical protection and ROS production under lipopolysaccharide administration, we found that superoxide dismutase activity decreased by 1.18 times, catalase activity did not change statistically significantly, and superoxide anion radical production increased by 1.61 times. The concentration of MDA increased by 2.16 times in the liver of rats compared to the control group. We did not observe statistically significant changes in the concentration of sulfide anion in the liver of rats under conditions of stimulation with bacterial lipopolysaccharide compared to the control group.

The effect of prolonged alcohol intoxication on the biochemical parameters of rat liver. Our previous studies have established that alcohol intake changes the activity of different isoforms of NOS from the first day of its excessive administration [28]. Prolonged administration of ethanol increased the activity of iNOS in the liver 4.5 times and cNOS rised 1.63 times compared to the control group. The concentration of $ONOO^-$ in the liver of rats increased 9.47 times, and the concentration of nitrites decreased by 1.26 times under conditions of prolonged alcohol intoxication compared to the control group. Concentration of S-NO decreased by 2 times, however, according to our previous studies, there was an increase in S-NO concentration on early terms of alcohol intoxication compared

Biochemical changes in the liver of rats under conditions of a combination of stimulation of the organism with bacterial lipopolysaccharide and alcohol intoxication (M ± m)

Biochemical parameters	Group			
	Control	Stimulation with lipopolysaccharide	Alcohol intoxication	Alcohol intoxication and stimulation with lipopolysaccharide
Inducible NO synthase, μmol/min per g of protein	0.16±0.02	0.30±0.02*	0.72±0.07*/**	0.54±0.08*/**
Constitutive NO synthases, μmol/min per g of protein	0.027±0.0003	0.039±0.0005*	0.044±0.0009*/**	0.108±0.0005*/**/***
Superoxide dismutase, c.u.	12.34±0.55	10.42±0.24*	12.23±1.03	21.22±1.61*/**/***
Catalase, μkat/g	0.376±0.008	0.376±0.008	0.230±0.01*/**	0.320±0.002*/**/***
Malonic dialdehyde, μmol/g	12.32±0.11	26.58±1.56*	15.91±0.32*/**	27.72±0.17*/**
Superoxide anion radical, nmol/s per g	1.84±0.004	2.96±0.04*	2.71±0.03*/**	4.07±1.08*/**
$ONOO^-$, μmol/g	0.45±0.01	4.32±0.14*	4.26±0.03*	4.34±0.04*/**
S-NO, μmol/g	0.36±0.019	0.21±0.007*	0.18±0.034*	0.15±0.013*/**
NO_2 concentration, nmol/g	7.14±0.17	3.85±0.13*	5.67±0.34*/**	5.37±0.17*/**
Sulfide anion, μmol/g	7.23±0.17	7.31±0.19	15.01±0.32*/**	5.03±0.53*/**/***

*P < 0.05 compared to control group; **P < 0.05 compared to stimulation with LPS; ***P < 0.05 compared to alcohol intoxication

with the control group [29]. Catalase activity decreased 1.63 times, superoxide dismutase activity did not change statistically significantly, superoxide anion radical production increased 1.47 times and malonic dialdehyde concentration increased 1.29 times in rat liver under conditions of prolonged alcohol intoxication compared to the control group. Thus, our studies confirm the general conclusion that the leading role in liver damage caused by alcohol intoxication is played by the development of oxidative stress.

Chen et al. [30] proved that the H_2S-mediated mechanism has a hepatoprotective effect on maintaining the integrity of hepatocytes under ethanol-induced oxidative stress. We discovered that the concentration of sulfide anion increased 2.08 times in the liver of rats under conditions of prolonged alcohol intoxication compared to the control group (Table).

The effect of lipopolysaccharide stimulation on the background of prolonged alcohol intoxication on the biochemical parameters of the liver of rats. Under the combined action of bacterial lipopolysaccharide and prolonged alcohol intoxication, we found that the activity of iNOS in the liver of rats increased 3.38 times compared to the control group and 1.8 times compared to the group of animals injected with bacterial lipopolysaccharide. The activity of cNOS in the liver of rats increased 4-fold under stimulation with bacterial lipopolysaccharide on the background of prolonged alcohol intoxication compared to the control group, 2.77 times compared to the group of animals injected only with lipopolysaccharide and 2.45 compared to the group of rats with prolonged alcohol intoxication (Table).

We found that the concentration of $ONOO^-$ in the liver of rats increased 9.64 times under conditions of stimulation with bacterial lipopolysaccharide on the background of prolonged alcohol intoxication compared to the control group. The concentration of nitrites in the liver of rats decreased 1.33 times under the combined effects of bacterial lipopolysaccharide and alcohol intoxication compared to the control group and increased 1.39 times compared to the group of animals injected only with bacterial lipopolysaccharide. The concentration of S-NO, which act as a buffer of nitric oxide, in the liver of rats decreased 2.4 times under the combined effects of bacterial lipopolysaccharide and alcohol intoxication compared to the control group and 1.4 times compared to the group of rats that received LPS injections.

By analyzing the development of oxidative stress in the liver of animals simulated by the combined effects of lipopolysaccharide and prolonged alcohol intoxication, we found that the activity of superoxide dismutase in the liver of rats increased 1.72 times compared to the control group. It was elevated 2.04 times compared to animals treated with bacterial lipopolysaccharide and 1.74 times compared to rats with prolonged alcohol intoxication. The activity of catalase in the liver of rats in the group of rats with a combined effect of bacterial lipopolysaccharide and alcohol intoxication decreased by 1.18 times compared to the control group and animals treated with bacterial lipopolysaccharide and increased 1.39 times compared to the rats with prolonged alcohol intoxication. The production of superoxide anion radical in the liver of rats in a group of rats with a combined effect of bacterial lipopolysaccharide and alcohol intoxication increased 2.21 times compared to the control and 1.5 times compared to the group of animals with prolonged alcohol intoxication. The concentration of malonic dialdehyde in the liver of rats in a group of animals with a combined effect of bacterial lipopolysaccharide and alcohol intoxication increased 2.25 times compared to the control and 1.74 times compared to the group of rats with prolonged alcohol intoxication. The concentration of sulfide anion in the liver of rats in a group of rats with a combined effect of bacterial lipopolysaccharide and alcohol intoxication decreased by 1.44 times compared to the control, 1.45 times compared with the group of animals injected with lipopolysaccharide and 2.98 times compared to rats with prolonged alcohol intoxication.

Based on the results of experimental studies, stimulation of rats with bacterial lipopolysaccharide against the background of excessive alcohol intake potentiates the production of superoxide anion radical against the background of imbalance of antiradical protection, accompanied by the development of oxidative stress and increases the intensity of lipid peroxidation. The concentration of MDA in group IV was significantly higher than in group III and did not differ from that in group II.

The activity of iNOS depends more on excessive alcohol intake than on stimulation by bacterial lipopolysaccharide, because the activity of iNOS in the group of alcohol intoxication and the combined effect of two pathogenic factors exceeds that in the group of rats administered lipopolysaccharide only. Therefore, the cause of nitric oxide hyperproduction in chronic alcohol intoxication may be the activation of the transcription factor NF-kB due to the destruction of hepatocytes caused by the accumulation of acetaldehyde after metabolic transformations of ethanol [31].

It should be noted that in vivo administration of bacterial lipopolysaccharide and chronic alcohol intoxication lead to the predominance of the conversion of nitric oxide into toxic peroxynitrite over the formation of its stable buffer forms (nitrosothiols). In this case, chronic alcohol intoxication leads to the accumulation of nitrites in the liver tissue, which may be associated with the accumulation of reduced electron donors ($NADH + H^+$ and $NADPH + H^+$), which is associated with the conversion of ethanol to acetaldehyde. Reduced proton donors can be used by nitrate nitrite reductases as coenzymes to reduce nitrates to nitrites.

The increase in the activity of constitutive isoforms of NO synthase in the studied groups may be associated with a decrease in the concentration of nitrosothiols. Nitrosothiols have the ability to regulate the activity of the endothelial isoform of NO synthase by nitrosylation of cysteine residues in the enzyme molecule [34]. Therefore, reducing the concentration of nitrosothiols can lead to increased enzyme activity.

CONCLUSIONS

1. Prolonged stimulation of the rat organism with *S. typhi* lipopolysaccharide, chronic ethanol intoxication and their combination lead to increased production of superoxide anion radical and reduction of antioxidant protection effectiveness, which causes oxidative damage to the liver of rats. Bacterial lipopolysaccharide enhances ethanol-induced oxidative damage to liver tissue by increasing the production of superoxide anion radical, that was observed despite the adaptive increase in the activity of antioxidant enzymes.

2. The production of nitric oxide in the liver of rats increases during prolonged stimulation of the rat organism with bacterial lipopolysaccharide of *S. typhi*, chronic ethanol intoxication and their combined effects. The predominant pathway of nitric oxide metabolism is the formation of peroxynitrite.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ВПЛИВ ЛІПОПОЛІСАХАРИДУ НА РОЗВИТОК ОКСИДАТИВНО-НІТРОЗАТИВНОГО СТРЕСУ В ПЕЧІНЦІ ЩУРІВ ЗА УМОВ ХРОНІЧНОЇ АЛКОГОЛЬНОЇ ІНТОКСИКАЦІЇ

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Метою нашої роботи було встановлення впливу стимуляції організму бактеріальним ліпополісахаридом *S. typhi* на розвиток оксидативно-нітрозативного стресу в печінці щурів за умов хронічної алкогольної інтоксикації. Дослідження проведене на 24 щурах-самцях лінії Вістар. Тварин рандомізовано розподілили на 4 групи по 6 тварин: I – контрольна; II – тварини, які отримували 0,4 мкг/кг бактеріального ліпополісахариду *S. typhi*; III – тварини, яким моделювали алкогольний гепатит та IV – тварини, яким моделювали хронічну алкогольну інтоксикацію та вводили бактеріальний ліпополісахарид *S. typhi*. Експеримент

тривав 63 доби. В гомогенаті тканин печінки досліджували продукцію прооксидантів, активність антиоксидантних ферментів, концентрацію сульфідного аніона, продукцію оксиду азоту та концентрацію малонового діальдегіду. Стимуляція організму бактеріальним ліпополісахаридом посилювала етаноліндуковане оксидативне ушкодження тканин печінки збільшенням продукції супероксидного аніон-радикала, незважаючи на адаптивне зростання активності антиоксидантних ферментів. Оксид азоту, продукція якого зростає в печінці щурів при тривалій стимуляції організму щурів бактеріальним ліпополісахаридом *S. typhi*, хронічній інтоксикації етиловим спиртом та їх поєднаному впливі, метаболізувалася переважно в пероксинітрит.

Ключові слова: ліпополісахаріднідукований гепатит; алкогольний гепатит; цикл оксиду азоту; сульфідний аніон.

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