Review article

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NITRATES AND NITRITES SIGNIFICANCE IN THE DEVELOPMENT OF ALCOHOLIC LIVER DISEASE

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Alcoholism is one of the most common addictions affecting health and the immune system in people worldwide. Chronic alcohol consumption over a prolonged period of time causes metabolic liver injury, along with arginine metabolism and nitric oxide (NO) synthase disorders. Ethanol intoxication under cumulative nitrooxidative and nitrosative stress conditions, as well as in inflammation, stimulates the production of NO anion (NO^-) and superoxide anion (O_2-), i.e. peroxynitrite formation in hepatocytes and endothelium. Mitochondrial dysfunction and disorders of adenosine triphosphate (ATP) molecules synthesis in hepatocytes cause disorders of intra - and extracellular antioxidants synthesis (glutathione and superoxide dismutase) and neutralization of toxic nitrates and nitrites. Peroxynitrites damage cell membranes lipoproteins, as well as the membrane enzyme systems and the mitochondrial matrix. They also damage the enzymes of ethanol and arginine metabolism in cytosol, and nucleic acid repair enzymes in hepatocytes. In the development of alcoholic liver disease (ALD), peroxynitrites cause reversible injuries of the structure and function of hepatocytes that proceed irreversibly, and vascular sinus endothelial damage, mediated by the mechanisms of apoptosis and necrosis.

Considering the fact that 3.3 million people die of ALD and its complications annually, the measures should be taken and aimed at reducing the onset, development, and progression of ALD. The priority is timely ALD diagnosis, as well as the severity of alcoholic liver damage. The studies have shown that the values of peroxynitrite elevation correlate with the severity of liver injury. It can be concluded that timely determination of peroxynitrite values followed by suitable antioxidant therapies may slow down the processes of hepatocyte apoptosis and necrosis, as well as the course of ALD.

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Introduction

Alcoholic liver disease is the third most common cause of death, after cardiovascular diseases and malignancies. According to the World Health Organization epidemiological data, the incidence of alcoholics in general population is about 5%, and in adult males it is about 10%. Excessive alcohol consumption over a longer period of time results in chronic liver damage.

Chronic alcohol consumption leads to liver damage. Alcohol-related liver diseases include alcoholic fatty liver disease, alcoholic hepatitis, and alcoholic cirrhosis. Alcoholic fatty liver disease and alcoholic hepatitis are reversible, but alcoholic cirrhosis is a non-reversible disease. Hepatocellular carcinoma is a severe complication of late-stage chronic liver disease. The severity of liver damage depends on the amount, concentration and duration of alcohol consumption (1). Alcohol toxicity is related to alcohol concentration. Weekly alcohol limit is cut to 14 units for women and men are advised not to take more than 21 units per week. One unit of alcohol is equal to a small glass of strong spirits, one glass of wine, or a half-pint glass of beer. Drinking more alcohol than the recommended safe limits for at least five years most certainly results in alcoholic liver disease. Liver injuries depend on factors that include genetic predisposition, nutritional status, gender, ethnicity, and social status. According to the World Health Organization data, 3.3 million of deaths resulted from harmful use of alcohol every year (2,3).

Alcohol primarily shows hepatotoxic effects. Acetaldehyde and reactive species play an important role in alcohol hepatotoxicity by the following biological mechanisms: the process of lipid peroxidation, protein covalent binding, activation of immunological mechanism, endotoxemia effects (4).

In oxidative stress, endotoxins released by gram-negative bacteria activate macrophages of the liver and blood. Macrophages inflammatory cytokines induce the expression of inducible nitric oxide synthase (iNOS). The peroxynitrite anion and hydroxyl radicals modify proteins, lipids, carbohydrates, and nucleic acid in cells by the process of nitrooxidative and nitrosative stress. Modification of these biomolecules results in their structural and functional changes, contributing to tissue and vascular endothelial injury. Irreversible hepatocyte damage and endothelial dysfunction cause hemodynamic disorders and the development of portal hypertension (5).

The mechanisms underlying the toxic effects of alcohol have not been fully understood yet. However, data collected from experimental and clinical studies show toxic effects of ethanol and its metabolites, as well as nitrates and nitrites toxicity, reflected by cumulative oxidative stress and antioxidant defense system exhaustion (6, 7).

Alcohol and oxidative stress in hepatocytes

Alcohol (ethanol) metabolism occurs in the liver by three enzymatic pathways: alcohol dehydrogenase (ADH), microsomal ethanol oxidizing system (MEOS) and catalysis (Figure 1).

The primary metabolic pathway of oxidative metabolism of ethanol is in cytosol by the cytosolic enzyme ADH. As the ethanol is oxidized, acetaldehyde is produced. The coenzyme nicotinamide adenine dinucleotide (NAD) is reduced and becomes nicotinamide-adenine-dinucleotide-hydrogen(NADH). Acetaldehyde enters the mitochondria where it is oxidized to acetate by acetaldehyde dehydrogenase (ALDH). The acetate is then involved in the Krebs cycle and broken down into water, carbon dioxide and acetyl CoA. Chronic alcohol consumption enhanced acetaldehyde production, as well as accumulation of reduced NAD (NADH) in the cytosol and mitochondria (8, 9).

Continuous alcohol intake induces microsomal ethanol oxidation in microsomes by the activity of the MEOS. In ethanol intoxication, the role of the MEOS in ethanol metabolism is much greater. The microsomal ethanol oxidizing system involves nicotinamide-adenine-dinucleotide-hydrogen-phosphate (NADPH) oxidase, cytochrome oxidase, and cytochrome P450-dependent enzyme. The ethanol inducible cytochrome P-4502E1 isoenzyme is responsible for ethanol metabolism. In ethanol intoxication, MEOS takes a role in ethanol metabolism. Stimulated activity of cytochrome P-4502E1 is a major pathway of oxidative stress in hepatocytes, producing great amounts of free radicals. Free radicals produced by microsomal NADH oxidase also include: hydroxyl radicals, hydroxyl ethyl radicals, superoxide radicals, and hydrogen peroxides (10). Significant amounts of superoxide radicals and hydrogen peroxide are produced in further metabolism of acetaldehyde by the activity of xanthine oxidase that is stimulated by reduced NAD and elevated NADH concentrations during the metabolism of ethanol into acetaldehyde. Acetaldehyde is highly reactive, it binds to cellular membrane lipoproteins, resulting in alteration of membrane fluidity. It causes structural and functional impairment of lipoproteins, as well as enzyme inactivation. Xanthine oxidase causes activation of carcinogenic substances (11).

The third pathway of ethanol oxidation occurs in peroxisomes by the activity of catalase and the presence of hydrogen peroxide. Oxidation of ethanol also produces acetaldehyde.

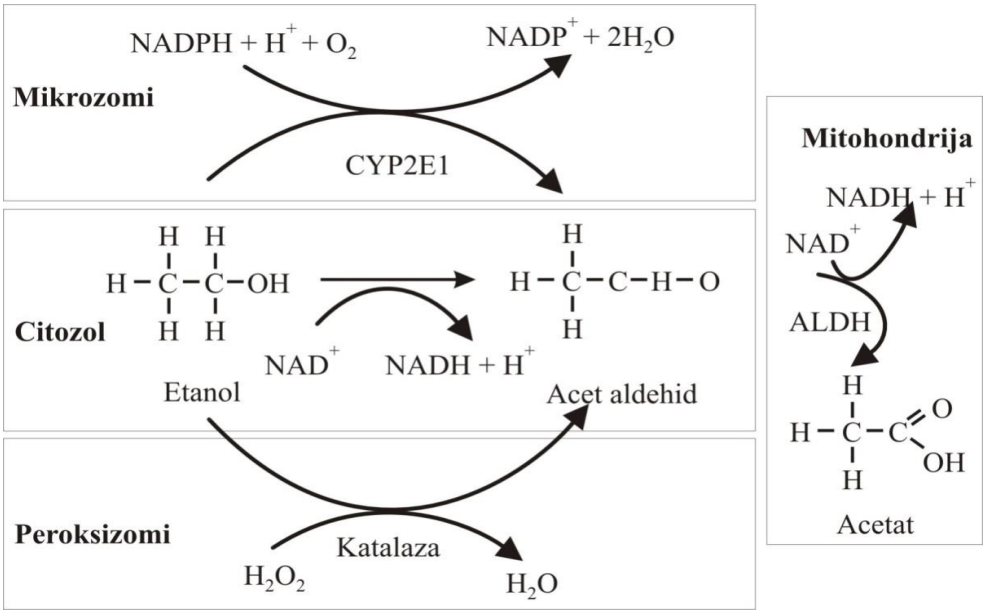

Figure 1. Ethanol metabolism

Ethanol metabolism as a source of reactive species

Ethanol metabolism is a significant source of reactive species generation. Reactive species are produced by ethanol and acetaldehyde metabolism during the following processes: microsomal induction, purine metabolism, stimulation of iron mobilization, increased concentrations of reduced NAD, and during the processes of neutrophils and macrophages stimulation. Reactive species are produced during ethanol metabolism, in enzyme reactions catalyzed by ADH, ALDH, microsomal cytochrome P-4502E1 oxidase, microsomal NADPH oxidase and microsomal xanthine oxidase (12, 13). Microsomes and mitochondria are the major source of reactive species production. The activity of the enzyme cytochrome P-4502E1 generates permanent free radicals and acetaldehyde. Microsomes and mitochondria have a primary role in ethanol oxidation. Hydroxyethyl radicals are generated by liver microsomes, involving cytochrome P-4502E1 induction. Alcohol induces production of superoxide radicals and hydrogen peroxide in mitochondria. Hydrogen atom abstraction from ethanol leads to production of hydroxyethyl radicals out of hydroxyl radicals:

$$CH_3CH_2OH + OH^- \rightarrow CH_3C^-HOH + H_2O$$

Hydroxyl ethyl radicals may react with oxygen and form peroxy radicals. Peroxy radicals reaction with molecular oxygen enables production of superoxide anion radicals:

$$CH_3C^-HOH + O_2 \rightarrow CH_3C(OO^-)HOH$$
$$CH_3C(OO^-)HOH \rightarrow CH_3CHO + O_2^- + H^+$$

Peroxynitrite radicals are formed in vivo from the reaction of nitric oxide and superoxide anion radical (14, 15).

Nitric oxide

Nitric oxide is an intercellular signaling molecule synthesized in blood vessels endothelial cells, macrophages, and other cells. It participates in regulation of a variety of physiological functions in the body, such as: regulation of vascular tonus, platelet aggregation, leukocytes adhesion, smooth muscle cells proliferation, apoptosis, and neurotransmission. The rate of nitric oxide diffusion through the cell membrane is rapid in almost all organs. Thus, it can control biological functions in the body. Nitric oxide is a highly reactive molecule. Biological reactivity of NO molecules is based on guanylyl cyclase, transformation into peroxynitrite, and interaction with thiol groups (16).

Nitric oxide synthesizes from L-arginine by the activity of NOS. This enzyme catalyzes the NADPH – dependent oxidation of L-arginine to NO, citrulline, and NADP (Figure 2). There are three NOS isoforms: the neuronal NOS (nNOSor NOS-1), inducible or inflammatory NOS (iNO Sor NOS-2), and endothelial NOS (eNOSor NOS-3). Endothelial and neuronal NOS isoforms are constitutive, Ca^{2+} dependent forms, while iNOS is Ca^{2+}independent NOS isoform. Functional eNOS has been identified in the liver sinusoidal endothelial cells and may contribute to local perfusion and portal pressure (17).

The activity of constitutive isoforms produces short-lived NO molecules. Nitric oxide is an important signaling molecule. There are many sources of NO production in the body. Nitric oxide is a primary mediator of liver cells injury; it also takes part in a potential protective mechanism against stimulants that cause cellular damage. The activity of iNOS produces large amounts of NO molecules for an extended period of time. The expression of iNOS is induced by cytokines and microbial products (18).

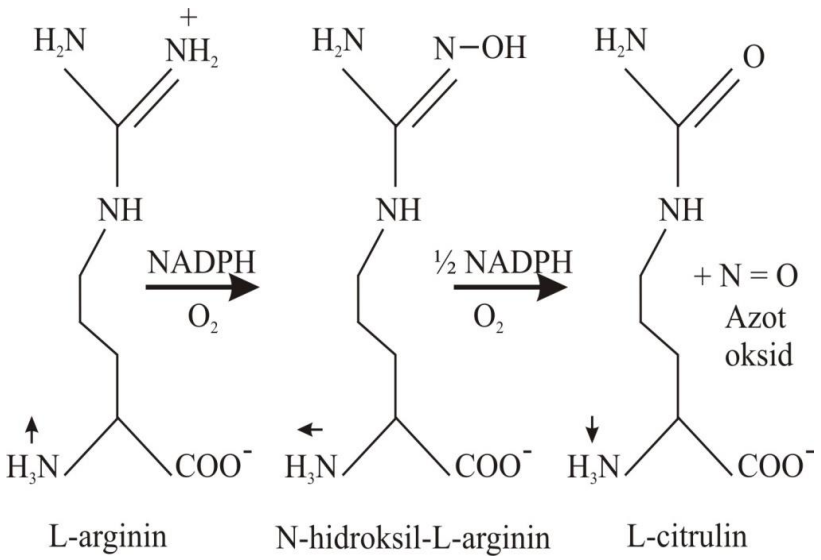

Figure 2. NO synthesis

Nitric oxide may have cytotoxic effects. Factors contributing NO cytotoxicity include localization and amount of NO generation, as well as the presence of oxidative stress, the amount of ROS, specific localizations of ROS (type of cells, intra - or extracellular localization). Peroxynitrite toxicity is manifested by interaction with biomolecules (19).

Nitric oxide and its metabolites may damage repair mechanism for nucleic acids. Peroxinitrites cause nucleic acids damage by activating inflammation and by the nuclear enzyme PARP mediation. Cell death occurs by necrosis and apoptosis (20). In the living organisms, the aggressive behavior of peryxonitrites is an important mechanism for the initiation and progression of a large number of acute and chronic diseases. Major NO cellular effects are illustrated in Figure 3.

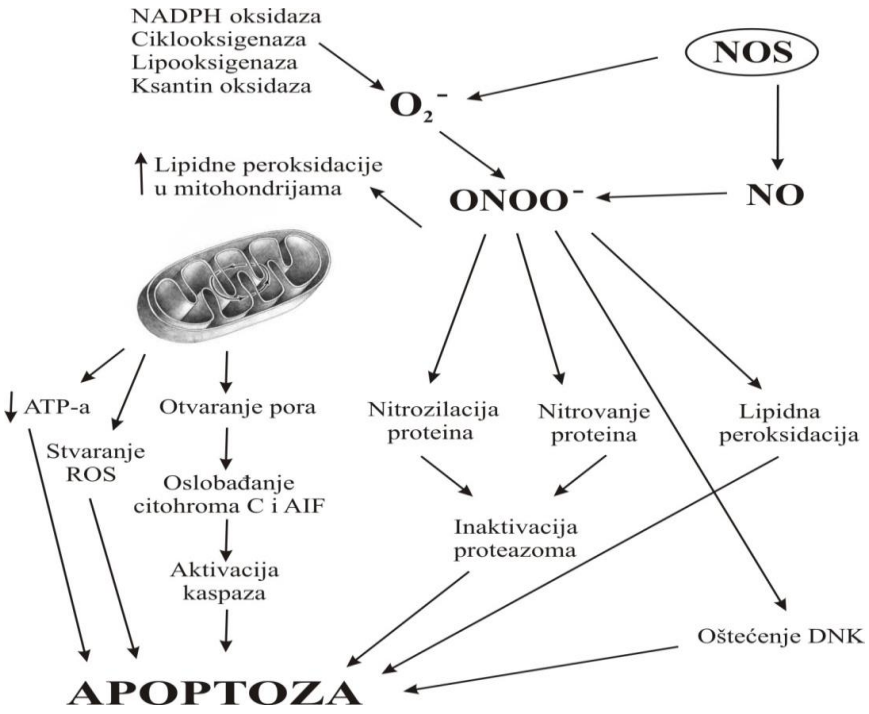

Figure 3. Major NO cellular effects

In the conditions of oxidative stress in liver damage, specific vasodilatory activity of eNOS is modulated or decreased. It leads to the development of increased intrahepatic vascular resistance. Thus, impaired microcirculatory perfusion occurs, as well as unequal necrosis in liver tissue as a consequence (21).

Nitric oxide is removed by rapid diffusion in the form of integrated complexes with erythrocytes. It is converted into nitrate by the reaction between NO and erythrocyte oxyhemoglobin. High concentrations of O_{2-} are quickly removed by deionization, by various superoxide dismutase (SOD) isoenzymes activities. In the living organisms, the aggressive behavior of peryxonitrites is an important mechanism for the initiation and progression of a large number of acute and chronic diseases.

Nitric oxide has a role in regulating ET-B endothelin receptor synthesis. In the conditions of ischemia-reperfusion and inflammation with endotoxemia, the roles of endothelin and its ET-B receptors change. Under the conditions of inflammatory stress, endotoxemia, ischemia and reperfusion in ALD, endothelin receptor gene expression is elevated, as well as ET-B receptors density, and endothelin level in the liver tissue (22, 23).

Peroxinitrites and mitochondria

Mitochondria are involved in hepatocytes vital processes, including energy production, calcium homeostasis and the control of biosynthetic pathways. Mitochondria also have an important role in the mechanism of cell death. Under the conditions of high NO production, peryxonitrites cause the impairment of mitochondrial function. Peroxynitrites react with mitochondrial components, thus having effects on every function of these organelles. Peroxynitrites enter the mitochondria from the extra mitochondrial space, or they may directly be produced in mitochondria. Mitochondria can produce NO by the activity of Ca^{2+} dependent mitochondrial NOS (mtNOS) (24). At the level of mitochondrial membranes, electron leakage from the respiratory chain causes pa-

rtial reduction of molecular oxygen to superoxide anion radical (O_2-). The role of NO in mitochondria is to regulate oxygen consumption by reversible inhibition of cytochrome C oxidase (complex IV of electron transport chain), by competing with oxygen, and by binding to binuclear site. During inflammation, reperfusion-ischemia in high NO production, electron transfer at the level of cytochrome C oxidase dysfunction is stimulated. Electron leakage from the respiratory chain occurs, as well as increased production of O_2- within the mitochondrial matrix and peroxynitrite (25, 26).

Peroxynitrites have a short half-life (10-20 ms). Peroxynitrite anion is highly diffusible. The injuries mediated by peroxynitrite are explained by its unique chemistry, including direct oxidation, nitrosative stress, as well as nitration reaction. Intensive processes of nitration and protein nitration lead to protein function modification. Peroxynitrites may directly oxidase low molecular weight thiols as well, such as GSH thiols (27).

Toxicity of peroxynitrites in mitochondria may result from direct oxidative reactions and ROS – mediated damage. Carbon dioxide (CO_2) is produced in mitochondria during decarboxylation in tri-carboxylic acid cycle. Carbon dioxide reacts with peroxynitrites. Direct reaction between peroxynitrites and CO_2 causes production of unstable nitrosoperoxycarbonates-that which quickly decompose into highly reactive radicals, carbonate radicals and NO radicals (26).

Peroxynitrites inhibit most components of the electron transport chain. Inhibition by peroxynitrites is achieved by different mechanisms: cysteine oxidation mechanism, nitration, tyrosine nitration, and iron-sulfur centers damage (27). Contrary to this, cytochrome C oxidase (complex IV), that is easily inhibited by NO, is resistant to peroxynitrites. Cytochrome C oxidase in its reduced form may act as an endogenous reduction catalyst of peroxynitrites into nitrites by its two electrons (28). The other target of peroxynitrites is cytochrome C that significantly decreases its redox properties by nitration. Nitration of cytochrome C increases its peroxidase activity that results in hydrogen peroxide production and exacerbation of oxidative damage of mitochondrial proteins (29).

Peroxynitrites additionally damage energy metabolism by the inhibition of aconitase enzyme, which inhibits tricarboxylic acid in mitochondria. Aconitase enzymes are found in mitochondrial matrix. Peroxynitrites inhibit aconitase enzymes via oxidative disruption of the 4Fe-4S center of the enzyme (30). Peroxynitrites also disturb energy metabolism by the inhibition of mitochondrial creatinine kinase that are present in the mitochondrial intermembrane space (31).

The reaction of peroxynitrite production is 3-fold faster than the reaction of SOD dismutation of O_2- to hydrogen peroxide. A 10-fold increase in O_2- and NO production causes 100-fold increased formation of peroxynitrites. However, under inflammatory conditions, O_2- and NO can be extremely increased by 1.000-fold, resulting in the increased formation of peroxynitrite by 1.000.000-fold. Superoxide dismutase is found in mitochondria, cytoplasm, and extracellular space. Superoxide dismutase is found in mitochondria, cytoplasm, and extracellular space. Decreased SOD activity, cycloxigenase, cyclooxigenase, xanthine oxidase accumulation of O_2- in cirrhotic liver, decrease of NO, increase of peroxynitrites in sinusoidal endothelial cells, increase of vascular resistance and the development of portal hypertension show that AOS therapy is significant in preventing hemodynamic disbalance in chronic alcoholic liver disease, ALD (32).

Peroxynitrites and apoptosis

Apoptosis is programmed cell death. Hepatocyte apoptosis is a typical consequence of increased peroxynitrite levels. Apoptosis is characterized by morphological changes, such as nuclear and cytoplasmic membrane condensation. The process of hepatocyte apoptosis results in the formation of small apoptotic bodies. Apoptotic bodies are membrane - bound particles that are quickly degraded by the phagocytes. Apoptosis is characterized by proteolytic cysteine protease activation, which is known as caspase. Caspase activity requires maintained ATP level. There are a few mechanisms that explain activation of programmed apoptosis by peroxynitrites, and they are greatly dependent on the cell type (33).

Apoptosis is activated by either death receptor activation (outer route), or by mitochondrial outer membrane permeabilization (inner route).

The common pathway of these two peroxynitrite-mediated apoptosis mechanisms includes outer mitochondrial membrane permeabilization. Permeabilization of the outer mitochondrial membrane enables the leakage of various proapoptotic signaling molecules that promote cellular apoptosis via caspase-dependent mechanisms, or caspase-independent mechanisms (34). Permeabilization of outer mitochondrial membrane may be activated by pore formation within the outer membrane by proapoptotic proteins (Bak, Bak1), by the process of anti-apoptotic protein inhibition, or by the phenomenon known as mitochondrial permeability transition (35).

Mitochondrial permeability transition is a pronounced characteristic of peroxynitrite-induced cell death. Mitochondrial permeability transition involves permeabilization of the inner mitochondrial membrane by a multiprotein complex, called permeability transition pores (PTP). The multiprotein complex consists of adenine nucleotide translocase, cyclophilin D, and the voltage-dependent anion channel. Formation of PTP occurs with calcium overload or by oxidative modification of critical thiol groups within nucleotide translocase. Permeability of transition mitochondrial pores causes the cessation of electrons transmission and ATP production. It occurs by the dispersion of mitochondrial membrane potential (36, 37).

In addition to direct effect on mitochondria, peroxynitrites may activate apoptotic mechanism by signal cellular modulation. A serine/threonine protein kinase has an important role, since its activation induces powerful protection mechanism to limit apoptosis in a variety of stressful conditions, including oxidative stress (38).

Peroxynitrites and necrosis

Hepatocyte necrosis occurs after cellular exposure to high concentrations of oxidants. Necrosis is associated with the exhaustion of cellular ATP capacity. Cellular ATP deficiency is a consequence of membrane disruption, the release of harmful degraded cellular substances, and the development of secondary inflammation. Many studies have shown that peroxynitrite-dependent cellular necrosis is mediated by a complex process, including DNA damage and activation of DNA repair enzyme (nuclear enzyme poly ADP-ribose polymerase PARP-1). The nuclear enzyme poly ADP-ribose polymerase enzyme system (PARP) is composed of PARP-1 and enzyme system poly ADP-ribose polymerase. The nuclear enzyme poly ADP-ribose polymerase type 1 detects and signals DNA strand breaks induced by different reactive species (hydrogen peroxide, peroxynitrites, nitrosyl anion and oxygen radicals, carbonate or hydroxyl radicals) (20).

Peroxynitrites-dependent cytotoxicity is mediated by lipid peroxidation, protein nitration and oxidation, DNA oxidative damage, activation of matrix metalloproteinase, and inactivation of a variety of enzymes in cells.

Inactivation of mitochondrial enzymes, as well as inhibition of ATP molecules synthesis, leads to mitochondrial swelling and increased permeabilization of mitochondrial membranes. Permeabilization of mitochondrial membrane causes the leakage of proapoptotic molecules, cytochrome C, and apoptosis-induced factor. In addition to harmful effects on mitochondria, peroxinitrites cause DNA breaks and induce severe oxidative damage to genomic DNA. DNA breaks are activated by nuclear enzyme PARP. Activated PARP depletes NAD to synthesize poly ADP-ribose polymerase (PAR). Mild DNA damage activates DNA repair mechanism.

In the case of moderate mitochondrial permeabilization and PARP activation, along with maintenance of cellular ATP, a cell may degrade by apoptosis. In reperfusion-ischemia, in very pronounced oxidative stress and nitrosative-induced DNA damage, cells can degrade by necrosis. Expressed mitochondrial permeabilization then occurs, as well as pronounced PARP activation, leading to massive NAD and cellular ATP exhaustion (39, 40).

In chronic, progressive liver disease there are differences in the degree of inflammation and fibrosis that originate from different nitrate and nitrite levels in blood. Recent studies have shown that an increase in NO_2 + NO_3 concentration is directly proportional to the degree of chronic liver injury. An increase in NO_2 + NO_3 concentration at the expense of peroxynitrite formation may be a causative factor for the development of cirrhosis and its complications in patients with cirrhosis (41).

In patients with cirrhosis, overproduction of nitrates and nitrites is involved in the pathogenesis of hepatic hemodynamic abnormalities development In end-stage liver cirrhosis with ascites, peroxynitrites and NO are key pathogenic factors responsible for the development of portal hypertension and its complications (42).

Conclusion

Alcohol abuse and ALD are global health problems. Considering the fact that 3.3 million people die of ALD and its complications annually, priority is given to timely diagnosis of ALD and alcoholic liver disease staging.

It can be concluded that the analysis of NO_2 + NO_3 values enhances the understanding of alcohol-induced liver disease pathogenesis, alcoholic liver disease staging, as well as monitoring of the disease progression. It can also be concluded that timely determination of toxic nitrates and nitrites values and suitable antioxidant therapy may slow down the processes of hepatocytes and vascular endothelial cells apoptosis and necrosis, i.e. the progression of ALD and hemodynamic disorder.

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NITRATI I NITRITI U RAZVOJU ALKOHOLNE BOLESTI JETRE

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Alkoholizam predstavlja jednu od vodećih bolesti zavisnosti koja štetno utiče na zdravlje i imunitet ljudi širom sveta. Hroničnim konzumiranjem alkohola u dužem vremenskom periodu nastaje poremećaj metaboličke funkcije jetre uz poremećaj metabolizma arginina i poremećaj sinteze azot oksida (NO). Pri etanolnoj intoksikaciji u uslovima kumulativnog nitrooksidativnog i nitrozivnog sresa, kao i inflamacije, nastaju NO anjon (NO^-) i super oksid anjon (O_2-), tj. peroksinitriti u hepatocitima i endotelu. Disfunkcija mitohondrija i poremećaj sinteze adenozin tri fosfata (ATP) molekula u hepatocitima dovodi do poremećaja sinteze intra - i ekstracelularnih antioksidansa (glutationa i superoksid dizmutaze) i neutralizacije toksičnih nitrita i nitrata. Peroksinitriti oštećuju lipoproteine membrana ćelija i sisteme enzima membrana i matriksa mitohondrija. Takođe, oštećuju enzime metabolizma etanola i arginina u citozolu i enzime reparacije nukleinske kiseline hepatocita. U razvoju alkoholne bolesti jetre (ABJ) peroksinitriti mehanizmima apoptoze i nekroze oštećuju najpre reverzibilno, a zatim ireverzbilno strukturu i funkciju hepatocita, kao i vaskularni endotel sinusa.

S obzirom da godišenje umire oko 3.3 miliona ljudi od ABJ i njenih komplikacija, treba raditi na smanjenju pojave i progresije ABJ. Prioritet predstavlja pravovremeno postavljanje dijagnoze ABJ, kao i dijagnoza stepena alkoholnog oštećenja jetre. Istraživanja pokazuju da vrednosti peroksinitrita rastu sa oštećenjem jetre. Može se zaključiti da pravovremeno određivanje vrednosti peroksinitrita, uz adekvatnu terapiju antioksidansima, može usporiti mehanizme apoptoze i nekroze hepatocita, kao i tok ABJ.

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Ključne reči: *alkohol, nitrati, nitriti, oštećenje jetre*