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REVIEW

FEATURES OF OXIDATIVE STRESS IN ALCOHOLISM

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The review considers molecular mechanisms underlying formation and development of oxidative stress (OS) in patients with alcohol dependence. The major attention is paid to the effects of ethanol and its metabolite acetaldehyde associated with additional sources of generation of reactive oxygen species (ROS) in response to exogenous ethanol. The own results of studies of the *in vitro* effect of ethanol and acetaldehyde on the concentration of peripheral OS markers — products of oxidative modification of proteins (protein carbonyls), lipids (lipid peroxidation products), DNA (8-hydroxy-2-deoxyguanosine, 8-OHdG) in blood plasma are presented. The changes in these parameters and the activity of antioxidant enzymes (SOD, catalase) in patients with alcohol dependence were analyzed. Own and literature data indicate that at a certain stage of the disease OS can play a protective rather than pathogenic role in the body.

Key words: oxidative stress; reactive oxygen species; peripheral markers of oxidative stress; ethanol; alcoholism

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INTRODUCTION

Pathological processes in the body are accompanied by oxidative stress (OS), a condition in which there is a steady increase in the stationary level of free radicals. The main chemical element involved in the formation of free radicals is oxygen. Molecular oxygen (O_2) plays a key role in a number of biochemical reactions of the mitochondrial respiratory chain, which provides necessary energy for the cell. During this process, (i) various oxygen radicals, including superoxide, are sequentially formed as intermediates; (ii) peroxide, which normally exists in cells as hydrogen peroxide; (iii) hydroxyl radicals. These unstable compounds are the main reactive oxygen species (ROS) [1, 2].

Ideas about the role of ROS in the body in modern terms and concepts were formulated at the end of the last the beginning of this century. However, there is no single definition of ROS. ROS is a collective concept that includes such compounds as (i) molecules — hydrogen peroxide (H_2O_2), ozone (O_3) and singlet oxygen ($^1O_2$); (ii) free radicals — superoxide anion ($O_2^{\bullet-}$), hydroxyl ($HO^{\bullet}$), perhydroxyl ($HO_2^{\bullet}$), peroxyl ($RO_2^{\bullet}$), alkoxyl ($RO^{\bullet}$); (iii) HO_2^- ion. ROS also include hypochlorous acid (HOCl), which, in fact, is the active form of chlorine, as well as peroxynitrite ($ONOO^-$) and nitric oxide ($NO^{\bullet}$), which are active forms of nitrogen [1, 3].

ROS are formed during the normal course of metabolism as a result of redox reactions and do not accumulate in the cell under physiological conditions. Along with other free radicals, ROS are involved in synthesis of prostaglandins, leukotrienes, thromboxanes, in the regulation of cell plasma membrane permeability, the functioning of transporters and receptor signal transduction, etc. [4, 5]. Protective reactions of innate immunity also include the generation of ROS [6]. However, the development of the pathological process is accompanied by an uncontrolled increase in the concentration of ROS leading to OS development. Free radicals interact with biological macromolecules and damage them; this leads to a decrease (or complete loss) of functional activity of these macromolecules and finally to cell death [5, 7-9]. ROS and OS are involved in the pathogenesis of almost all diseases [10] and therefore OS may be considered as a universal mechanism of damage to various macromolecules, regardless of the type of pathology. In the pathogenesis of mental illness and diseases associated with the use of psychoactive substances, OS also plays an important role.

1. ALCOHOL AND ADDITIONAL SOURCES OF GENERATION OF REACTIVE OXYGEN SPECIES

OS developed in mental and behavioral disorders induced by alcohol consumption (alcohol dependence, alcoholism) has its own characteristic features. Thing is that alcoholism is a pathology formed as a result of the chronic use of ethanol, which is not a foreign substance for the human body. Results of studies convincingly indicate that the level of endogenous ethanol varies in people of different races living in different regions of the planet. The blood concentrations of endogenous ethanol in residents of central Russia range

from 0.05 mmol/l to 0.2 mmol/l [11]. The biological role of endogenous ethanol is diverse: it participates in maintaining the liquid crystalline state of the lipid bilayer of membranes, in the regulation of cholesterol synthesis, and indirectly participates in the functioning of the regulatory systems of the cell and the whole organism [11, 12].

Exogenous ethanol, entering the body, is rapidly absorbed into the blood through the mucous membranes of the gastrointestinal tract and is distributed throughout the body proportionally to the water content in the tissues. Elevated concentrations of ethanol in a certain way influence many biological processes; however, no single known mechanism of action at the molecular level can explain all the effects that ethanol has on a particular organ and the whole organism. The resultant effect of alcohol is cumulative and includes many direct and indirect effects.

Ethanol is highly soluble in both hydrophilic and hydrophobic media. It has a membranotropic effect on various biological membranes (neurons, erythrocytes, myelin and mitochondrial membranes, synaptosomes), as well as artificial membranes. Dissolving in water and partially in the lipid bilayer of membranes, the ethanol molecule is introduced into the surface region between the polar groups of phospholipids. This causes a decrease of the packing density of phospholipids accompanied by the increase in the membrane fluidity, which facilitates the oxygen access to double bonds of unsaturated fatty acids, thus facilitating activation of lipid peroxidation (LPO) processes [13]. Prolonged intoxication with ethanol has a significant impact on membrane transport, on the systems of transmembrane information transfer, and on the activity of membrane-bound enzymes.

Severe metabolic impairments in chronic alcohol intoxication affect the functioning of organs and systems of the whole organism. Ethanol abuse leads to liver diseases (cirrhosis, hepatocellular carcinoma), cardiovascular diseases (cardiomyopathy, coronary heart disease, ischemic stroke, arterial hypertension), damage of the pancreas, pathology of the kidneys, respiratory organs and endocrine system, impaired function of the immune system, myopathies, osteoporosis, neurological and mental diseases, including fetal alcohol syndrome and alcohol dependence. Convincing evidence exists that chronic use of ethanol contributes to the development of oncological diseases, associated with its ability to dissolve carcinogens, as well as the fact that its main metabolite, acetaldehyde, is itself a carcinogen and has a mutagenic effect, damaging DNA [14].

The factor that largely determines the toxic effects of ethanol is its ability (as well as the ability of acetaldehyde) to generate excessive formation of free radicals, including ROS; this influences the redox status of cells, accompanied by the development and maintenance of OS at a high level. Thus, in addition to the general mechanisms of OS development, alcoholism is characterized by specific features associated with additional sources of ROS generation due to activation of oxidative reactions upon the exogenous ethanol intake [15-19].

The main processes and pathways involved in increased ROS production under the influence of chronic intake of high doses of ethanol are presented in the Table 1.

Let us consider each of these pathways in more detail.

Table 1. The pathways of ethanol-mediated increase in ROS concentration in the body

No.	Processes involved in the ethanol-mediated increase in ROS production	The main references
1	Metabolism of ethanol and acetaldehyde results in ROS generation in the body	[21-24, 27, 28]
2	Ethanol induces mitochondrial dysfunction, which results in shifts in the functioning of the respiratory chain, a decrease in ATP production and an increase in ROS	[32, 34, 37, 38]
3	Ethanol induces the conversion of xanthine dehydrogenase to xanthine oxidase producing ROS	[39, 40]
4	Ethanol can change the concentration of certain metals in the body, thus promoting ROS production	[42-44]
5	Ethanol can reduce the level of antioxidants eliminating ROS	[16, 50, 51, 53]
6	Ethanol changes the activity of antioxidant enzymes that ensure a stable level of ROS in the cell	[55, 58-60, 64, 65]

1.1. Metabolism of Ethanol and Acetaldehyde in the Body Leads to the ROS Production

Ethanol is metabolized in the body by a special enzymatic system responsible for its oxidation. This system includes alcohol dehydrogenase (ADH), cytochrome P450 (ethanol induces a special isoform of cytochrome P450 — P450-2E1 or CYP2E1) and catalase. ADH is the most important enzyme for ethanol metabolism. Under the action of ADH, ethanol is converted into a highly reactive acetaldehyde. This transformation is accompanied by an increase in the production of ROS and their accumulation in the body. Under the action of ADH with the participation of the NAD^+ cofactor, 75-90% of the incoming ethanol is oxidized. ADH is localized in the cells of almost all organs — kidneys, endocrine glands, brain, liver, gastrointestinal tract, etc. However, the major proportion of this enzyme is located in the cytosol of liver cells [20]. The process of ethanol metabolism and ROS formation in the hepatocyte is shown in Figure 1 [21].

The ethanol-induced cytochrome P450 isoform CYP2E1, which plays an important role in protecting the body from the toxic effects of alcohol, is also involved in the formation of ROS. CYP2E1 is especially active in the production of hydrogen peroxide and superoxide anion radicals, so it is of particular interest in the study of alcohol-induced OS [22-24].

Catalase is involved in the metabolism of ethanol with the formation of acetaldehyde and water; ethanol interaction with the catalase-H_2O_2 complex can generate ROS. Cytochrome P450 and catalase have long been considered as minor alternative pathways for ethanol oxidation [25, 26]. However, according to new data, these pathways may be more important for the oxidative metabolism of ethanol than it was previously thought [27].

The main metabolite of ethanol, acetaldehyde, has pronounced toxic properties; it can cause various structural and metabolic disorders in the cell. It is oxidized mainly in liver mitochondria by NAD^+-dependent acetaldehyde dehydrogenase,

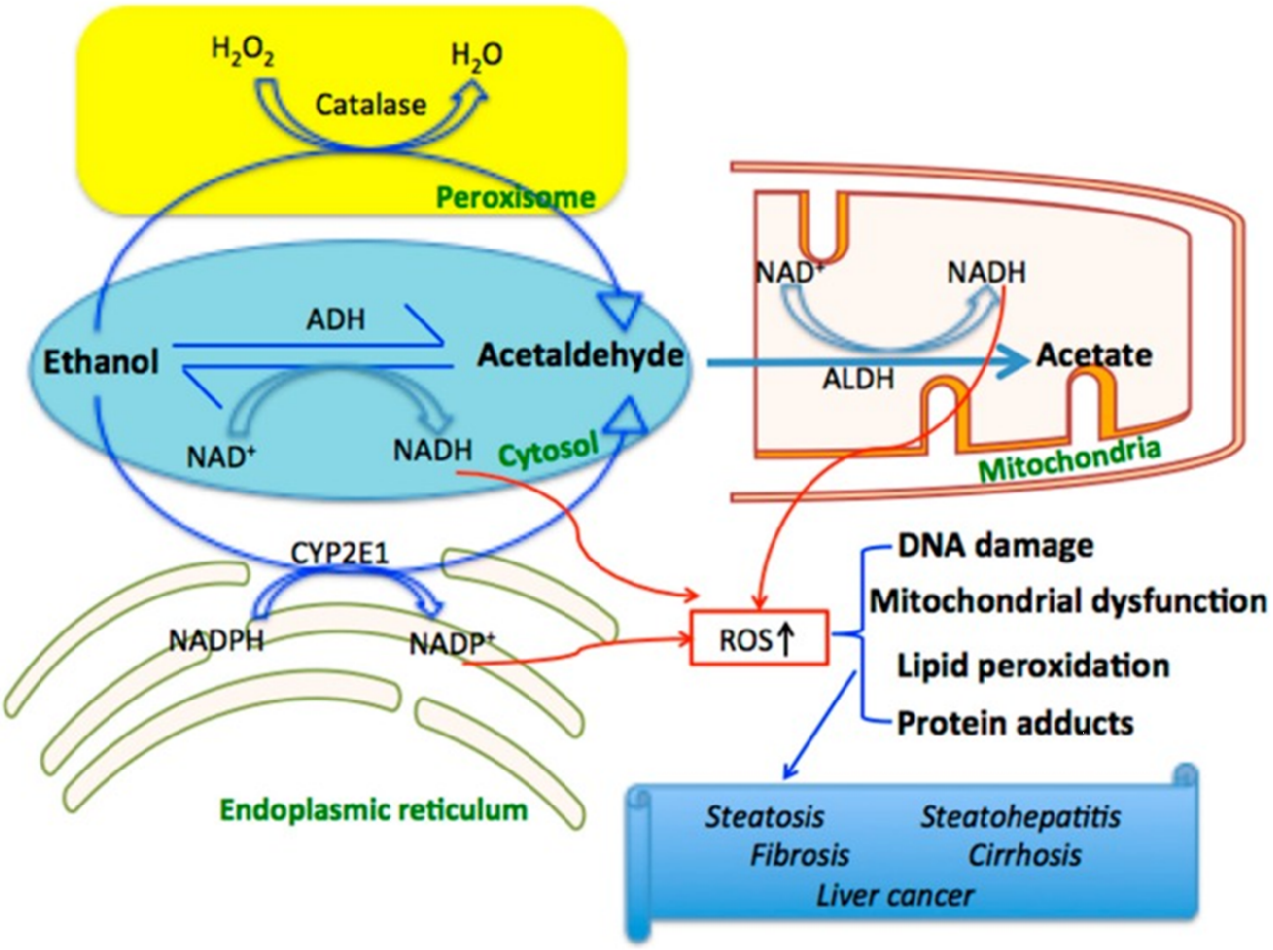

Figure 1. Oxidative metabolism of ethanol in the hepatocyte and the ROS formation (an open access license) [21]. Abbreviations: ROS, reactive oxygen species; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P450-2E1.

catalyzing acetaldehyde conversion to acetic acid, after that it is further degraded to CO_2 and H_2O. Under conditions of increased acetaldehyde concentration, FAD-dependent aldehyde oxidase is induced, and in the course of the reaction, in addition to acetic acid, hydrogen peroxide and other ROS are formed; this is another factor contributing to the development of OS in chronic alcohol intake [20, 28]. The role of acetaldehyde in the toxic effects of ethanol and the main molecular mechanisms in which acetaldehyde is involved in triggering oxidative stress are discussed in more details in [29-31].

Thus, during the oxidation of high concentrations of ethanol, the levels of acetaldehyde and acetate significantly increase; this is accompanied by the ROS increase, and changes in the ratio of reduced and oxidized forms of coenzyme dehydrogenases ($NADH/NAD^+$) due to the accumulation of NADH.

1.2. Ethanol Impairs Mitochondrial Function, which Leads to Significant Shifts in the Functioning of the Respiratory Chain, a Decrease in ATP Production, and an Increase in ROS

Mitochondria are one of the main sources of ROS in many cell types. These organelles concentrate most of the oxidative metabolic pathways and, therefore, contain numerous redox carriers and centers potentially capable of one-electron reduction of oxygen to radicals [1, 32].

Alcohol intoxication leads to a change in the respiratory and ATP-synthesizing activity of mitochondria, to significant functional changes of mitochondrial enzyme systems, such as the respiratory chain, enzymes of fatty acid oxidation and the urea cycle, as well as to alterations in the ultrastructure of these organelles [33]. All stages of ethanol oxidation are accompanied by NAD^+ reduction. The excess of reducing equivalents formed during ethanol oxidation (NADH) facilitates the transfer of unpaired electrons to oxygen with the formation of the superoxide anion [34]. The main sites of ROS formation in the mitochondrial electron transport chain are complexes I and III (NADH dehydrogenase and ubiquinone cytochrome *c* reductase, respectively). Chronic ethanol intake is accompanied by a significant decrease in the rate of mitochondrial respiration on both NAD^+- (glutamate/malate) and FAD^{2+} (succinate) dependent substrates. Since the effect of ethanol is more pronounced on NAD-dependent substrates, this indicates that ethanol preferentially influences complex I of the respiratory chain [35]. Acetaldehyde also inhibited the mitochondrial respiratory chain at the site between pyridine nucleotides and flavoproteins and decreased all redox processes in mitochondria followed by disruption of ATP synthesis in oxidative phosphorylation reactions [36].

The effect of alcohol intoxication on mitochondria has been studied in details using liver mitochondria. Ethanol can exhibit direct toxic effects on mitochondrial membranes; in addition, ethanol can act on mitochondria indirectly, when the toxic effect is determined by the product of ethanol oxidation (acetaldehyde and/or elevated ROS concentrations) [37]. In the other study, mitochondria are considered as one of the main mediators of ethanol-induced neurotoxicity, while ROS play a significant role in the manifestation of the effects of ethanol [38].

1.3. Ethanol Induces Conversion of Xanthine Dehydrogenase to Xanthine Oxidase Generating ROS

ROS are produced by various oxidative cellular enzymes, including xanthine oxidase. Under normal physiological conditions, this enzyme acts as a dehydrogenase catalyzing the reaction of NAD^+-dependent dehydrogenation of xanthine or hypoxanthine. However, under certain conditions, such as impaired blood flow to the tissue (hypoxia), xanthine dehydrogenase is converted to a ROS-producing oxidase. Ethanol consumption also promotes conversion of xanthine dehydrogenase to xanthine oxidase. *In vitro* experiments have shown that the conversion of dehydrogenase into oxidase is provided not by ethanol, but by acetaldehyde, i.e., xanthine dehydrogenase conversion to xanthine oxidase requires biotransformation of ethanol [39]. In the oxidase form, the affinity of the enzyme for NAD^+ is significantly reduced, while for oxygen affinity increases; this leads to one- and two-electron reduction of O_2 with the formation of superoxide anion and hydrogen peroxide, enhancing OS [39, 40]. The involvement of the xanthine oxidase pathway in the development of OS under the influence of ethanol is confirmed by results of studies on the effect of the xanthine oxidase inhibitor, allopurinol, on the biochemical and morphological manifestations of the ethanol action [41]. Administration of allopurinol to rats exposed to alcoholization was accompanied by a twofold decrease in the activity of blood aminotransferases, inflammatory and necrotic signs and a 40% decrease in the the production of free radicals. It is possible that the ethanol-induced conversion of xanthine dehydrogenase to the ROS-producing form (xanthine oxidase) is also associated with hypoxic phenomena observed during ethanol administration.

1.4. Ethanol Can Change Concentrations of Certain Metals in the Body, thus Promoting ROS Production

Transition metals play an important role in ROS production. Information about metal-mediated formation of free radicals, the role of OS in metal toxicity, and the effect of metal-induced ROS formation and oxidative modification of biomolecules

on the development of various human diseases have been summarized in several reviews [42, 43]. Transition metals, particularly iron and copper, have been shown to promote ROS-mediated cell damage and OS development, as they increase the formation of hydroxyl radicals in biological systems. Since iron ions play a critical role in the formation of hydroxyl radicals, all factors increasing the level of free iron in cells contribute to the formation of ROS and OS development. Chronic ethanol consumption increases the level of iron in the body (it enhances the iron absorption from food). Animal studies have shown that the addition of iron to ethanol-containing diets exacerbates liver damage, while administration of agents that trap free iron can prevent or attenuate the toxic effects of ethanol on the liver [16, 44].

1.5. Alcohol May Reduce Levels of ROS-Eliminating Antioxidants

The level of ROS in the cell is controlled by special mechanisms that protect it from the toxic effects of free radicals and maintain the overall balance and homeostasis in the body. Under physiological conditions, oxidative processes are under the strict control by a specialized cell system (the endogenous antioxidant system), which includes various, both enzymatic and non-enzymatic mechanisms that maintain a steady state level of ROS [1, 8]. Some of these mechanisms are impaired after drinking alcohol, which also contributes to cell damage in various organs.

Non-enzymatic antioxidants that play a certain role in protecting the body from excessive accumulation of ROS include peptides and proteins that do not have enzymatic activity. These include, first of all, the tripeptide glutathione (GSH), as well as albumin, transferrin, ferritin, lactoferrin. In addition, non-enzymatic antioxidants include ubiquinone, bilirubin, uric acid, steroid hormones, carotenoids, vitamin E (α-tocopherol), vitamin A (retinol), and vitamin C (ascorbate) [8].

Vitamin E is the main antioxidant contained in the lipid phase of membranes and acts as a powerful LPO inhibitor. The reaction between vitamin E and the lipid radical produces a vitamin E radical, which can be reduced in a reaction involving GSH and ascorbate. Vitamin E can prevent most metal-mediated (iron, copper, cadmium) damage both in *in vitro* systems and in metal-loaded animals [42]. Patients with alcoholic liver disease are characterized by decreased levels of vitamin E levels [16].

Vitamin C (ascorbic acid, ascorbate) can reduce the α-tocopheryl radical, thereby restoring the antioxidant properties of vitamin E. However, in the presence of iron or copper ions, ascorbate can exhibit prooxidant properties; however, according to other reports, vitamin C in the presence of these metals and hydrogen peroxide is able to prevent lipid peroxidation and oxidation of blood proteins [42]. It has also been shown that ascorbic acid accelerates ethanol metabolism and excretion from the body [45]. *In vitro* experiments have shown that lithium ascorbate protects blood plasma proteins and lipids from ethanol-induced oxidation [46].

In general, formation of alcohol dependence is usually accompanied by vitamin deficiency. For example, it has been shown that prolonged use of ethanol accelerated metabolism of vitamins A, D, E and a decrease in their content in the body was associated with activation of cytochrome P450-2E1 [25]. During chronic ethanol use, vitamin deficiency plays an important role in the development of numerous functional impairments in the peripheral and central nervous system [47].

Glutathione (GSH) is the most important non-enzymatic antioxidant present in cells. It is involved in many biological processes, including the detoxification of xenobiotics, the removal of substances that react with oxygen, the regulation of the redox balance in cells and the oxidative state of important protein sulfhydryl groups, and the regulation of immune functions [48]. Possible causes and consequences of the imbalance between GSH and ROS are discussed in detail in the review [49]. Based on the analysis of a large number of scientific reports, the authors have characterized the factors responsible for the disruption of the cellular balance of ROS and GSH, leading to cell death [49].

In patients with alcohol withdrawal, there was a significant decrease in blood plasma GSH [50], as well as a decrease in the GSH concentration and a 1.5-fold increase in glutathione peroxidase activity in the osmotic hemolysate of erythrocytes [51]. The reason for such disturbances in GSH metabolism may be the formation of glutathione adducts with unsaturated reactive aldehydes, which are formed during LPO processes [52]. Ethanol caused a decrease in the level of glutathione in mitochondria normally characterized by a high level of GSH required for elimination of ROS generated during respiratory chain functioning. Mitochondria cannot synthesize GSH; they import it from the cytosol by using a carrier protein localized in the mitochondrial outer membrane. It is suggested that ethanol impairs the function of this protein and this leads to mitochondrial GSH depletion [16]. A certain contribution to the change in glutathione metabolism and the total antioxidant capacity of the blood is also made by a significant increase of glutathione S-transferase during alcohol withdrawal, in which increased consumption of GSH probably occurs [53]. In addition, ethanol administration to rats caused an increase in the rate of catabolism of cysteine to taurine; this can also contribute to a decrease in GSH in liver cells due to substrate-dependent impairments of glutathione biosynthesis [54].

1.6. Ethanol Influences Activity of Antioxidant Enzymes Maintaining a Stable Level of ROS in the Cell

Mechanisms involved in the regulation of antioxidant enzymes activities induced by the alcohol influence are very diverse and, at the same time, universal. This is due to the fact that enzymes are protein molecules, and when they interact with ROS, excessively generated as a result of high doses of ethanol consumption, their structure can be modified and functional activity inevitably changed [16, 17]. Antioxidant enzymes that control ROS levels include superoxide dismutase (SOD), catalase, and glutathione peroxidase.

SOD is a group of metalloenzymes that catalyze the dismutation reaction of superoxide anion radicals. They maintain the concentration of these radicals in the cell at a low level, and also reduce the probability of the formation of singlet oxygen. The latter is especially important because activity of singlet oxygen is 3-4 orders of magnitude higher than the activity of superoxide anion radicals. Contradictory data exist regarding the effect of chronic alcohol exposure on cellular and extracellular SOD content or activity: there are reports about an increase, lack of changes or a decrease of these parameters depending on the experimental model, diet, amount and duration of alcohol consumption, etc. In the case of the intragastric ethanol infusion model, most frequently used in experiments with rats and mice, a decrease in the liver SOD activity was found [55].

In another study, no significant differences were found in the liver SOD activity between the groups of control and ethanol-treated rats [56]. The *SOD1* gene expression insignificantly changed in the rat liver 24 h after ethanol administration [57]. In patients with alcohol withdrawal, SOD activity in plasma was higher than in healthy donors, while in erythrocytes it did not differ from the control [58, 59]. At the same time, traditional anti-alcohol therapy for 7 days did not have a noticeable effect on SOD activity both in blood plasma and in erythrocytes of patients [59]. Increased activity of SOD in serum of alcoholic patients was also reported by other authors [60]. However, a number of studies have found that at an early stage of alcohol withdrawal, serum SOD activity decreased for at least a 2-week period [61, 62].

Catalase is a heme-containing enzyme found primarily in small cellular components known as peroxisomes, as well as in the cytosol of erythrocytes, where it promotes hydrogen peroxide removal. Catalase eliminates hydrogen peroxide by catalyzing a reaction between two molecules of hydrogen peroxide yielding water and O_2. In addition, catalase promotes interaction of hydrogen peroxide with compounds that can serve as hydrogen donors, so that hydrogen peroxide can be converted into one water molecule, while the reduced donor is oxidized (a process sometimes called catalase peroxidase activity) [63]. Various compounds (including ethanol and other alcohol) can provide these hydrogen atoms. According to numerous literature data, the catalase activity in plasma (serum) of patients with alcoholism depends on many factors and varies ambiguously. At the early stage of alcohol withdrawal syndrome catalase activity was comparable to control [61]. Another study found an increase in blood plasma catalase activity in patients with ethanol withdrawal [64]. Other authors reported increased catalase activity in serum of patients with post-acute withdrawal syndrome [65]. There is also evidence of decreased activity of catalase in patients with alcohol withdrawal compared with participants in the control group [60].

The glutathione peroxidase system consists of several components: the enzymes, including glutathione peroxidase and glutathione reductase, as well as cofactors (GSH and NADPH). There are several isoenzymes that differ in cellular localization and substrate specificity. Glutathione peroxidases catalyze the reduction of hydrogen peroxide to water and lipid hydroperoxides to the corresponding alcohols and glutathione. GSH is an important component of this system; it serves as a cofactor for the enzyme glutathione transferase. This enzyme helps remove drugs and chemicals, as well as other active toxic molecules from cells. Moreover, GSH can directly interact with certain ROS (for example, the hydroxyl radical), providing their detoxification [66].

In general, it is not possible to make an unambiguous conclusion about the direction of the effect of alcoholization on the activity of antioxidant enzymes. This direction depends on such factors as the age of the patient, the quantity and quality of alcohol consumed, the duration of its use, the quality of nutrition, somatic burden, the intake of pharmacological drugs, etc. At the same time, the published data show that ethanol can disrupt the functioning of almost all links of the antioxidant system, which inevitably leads to the accumulation of ROS.

2. ETHANOL AND OXIDATIVE DAMAGE OF MACROMOLECULES

At high concentrations, ROS can interact with each other, forming highly reactive radicals that are also capable of oxidizing cellular structures and further depleting the antioxidant system. The toxicity of high concentrations of ROS is largely related to their ability to react with most macromolecules, including proteins, lipids, and DNA [67]. In this case, the products of oxidative modification of macromolecules, which are considered to be OS biomarkers, accumulate in the body [68, 69].

The scheme (Fig. 2) shows the products of oxidative damage of proteins, lipids, and DNA (OS markers) and consequences of their accumulation in the cell.

2.1. Products of Oxidative Damage of Macromolecules are OS markers

Oxidative modification of proteins primarily damages amino acid residues that are most sensitive to ROS. Cysteine, methionine and histidine are readily oxidized by the hydroxyl radical. Enzymes in which these amino acid residues are localized in the active site will be inactivated after interaction with ROS. In addition, ROS-induced oxidation of proteins can lead to changes in their three-dimensional structure, as well as to their fragmentation, aggregation, or cross-linking. Finally, oxidation increases susceptibility of the oxidatively modified protein to degradation by the cellular systems responsible for elimination of damaged proteins from the cell [5].

One of the main types of oxidative modification of proteins is their carbonylation. Carbonyl groups can be formed by oxidative damage to amino acid residues with free carboxyl groups, cysteine residues containing SH-groups. However, the α-amino groups and ε-amino groups of lysine, guanidine groups (arginine), imidazole (histidine) and indole groups (tryptophan) are predominantly oxidized. When carbonyl groups (=C=O) interact with nucleophilic amino groups ($-NH_2$) of amino acids, cross-linking of proteins is observed; this leads to the formation of high-molecular protein aggregates and impaired functioning of proteins and the whole cells [5]. Another type of oxidative modification of proteins is their glycation: non-enzymatic interaction of glucose with free amino groups of proteins. Under conditions of hyperglycemia (in particular, in diabetes mellitus), the glycation process is accelerated, resulting in the formation of glyoxal, methylglyoxal, and 3-deoxyglucosone, which trigger the process of oxidative glycation of proteins with the ROS formation [70]. In alcoholism, the level of glycated blood proteins increases [71].

Under conditions of OS lipids are also subjected to oxidative modification. First of all, this includes LPO: intensive autoxidation of unsaturated fatty acids (linolenic, arachidonic, etc.) of biological membrane phospholipids. Under conditions of LPO intensification, fatty acid residues of phospholipids are oxidized to hydroperoxides. This changes the package of membrane lipids and leads to damage to the structure and permeability of cell membranes. One hydroxyl radical can cause peroxidation of many molecules of polyunsaturated fatty acids, because the reactions involved in this process are part of a cyclic chain reaction. In addition to cell damage by destroying membranes, LPO initiates the formation of reactive products that can react with and damage proteins and DNA. The formation of lipid peroxides, which are easily subjected to further transformations, leads to the formation and accumulation of a number of more stable secondary oxidation products: aldehydes, ketones,

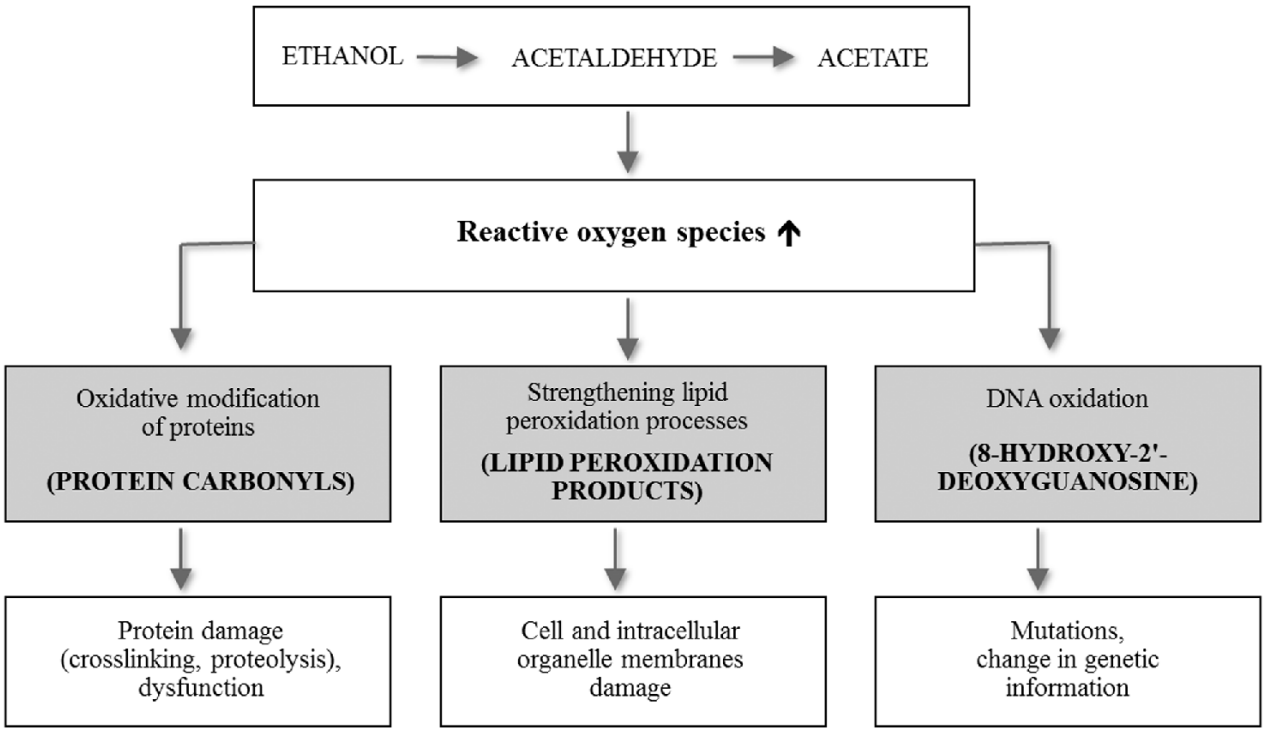

Figure 2. Markers of oxidative stress – protein carbonyls, lipid peroxidation products, 8-hydroxy-2′-deoxyguanosine.

low molecular weight acids (formic, acetic, butyric), epoxy compounds, etc. These substances are toxic to the cell; they lead to impairments in membrane functions and metabolism in general. Polyunsaturated fatty acids peroxides, dialdehydes, and a number of LPO secondary products, interacting with the N-terminal groups of amino acids of proteins, form Schiff bases, which further lead to intermolecular "cross-links" [72].

DNA is the genetic material of the cell, and any irreversible damage to the DNA can lead to changes in the proteins coded for by the DNA. This, in turn, leads to dysfunction of proteins or even to their complete inactivation. Although cells have repair mechanisms to correct naturally occurring changes in DNA, additional excessive damage induced by ROS can lead to irreversible changes with extremely negative consequences [5]. Mitochondrial DNA is especially sensitive to OS, since, unlike nuclear DNA, it is not protected by histones and is localized near the inner mitochondrial membrane, the main site of ROS generation [37]. It has been shown that ethanol causes damage of mitochondrial DNA by the OS-mediated mechanism [73].

The products of DNA oxidative modification are most often detected by means of a sensitive analytical method for assessing 8-hydroxy-2′-deoxyguanosine (8-OHdG). Despite the fact that more than 30 products of oxidative modification of nitrogenous bases of nucleic acids are known, the product of guanine oxidation that is determined most frequently. This is due to the fact that guanine in DNA has the lowest redox potential among natural nitrogenous bases; therefore it is easily oxidized at the C8 position. In this case, 8-oxo-dihydroguanine is formed, the redox potential of which is even lower; this leads to its further oxidation to the stable product 8-OHdG [74].

2.2. Damage of Plasma Macromolecules Induced by Ethanol and Acetaldehyde in Vitro and in Patients with Alcoholism

In order to elucidate the role of ethanol and acetaldehyde in oxidative damage of macromolecules in alcoholism, blood samples of healthy men were incubated with ethanol or acetaldehyde *in vitro*. This exposure led to damage to erythrocyte membranes [75, 76] and an increase in the products of oxidative modification of proteins and lipids in plasma [76, 77]. These studies used 0.5% ethanol and 0.01% acetaldehyde. Incubation of control samples (without ethanol or acetaldehyde) during 3 h at 37°C was accompanied by a significant increase in the level of carbonylated proteins and LPO products versus zero time. This implies spontaneous oxidation of proteins and lipids in these samples.

The addition of ethanol led to a significant increase in oxidized macromolecules: thus, ethanol induced oxidative modification of both proteins and lipids in human plasma. The addition of acetaldehyde to blood samples also led to an increase in the concentration of measurable OS markers in plasma. At the same time, in contrast to the samples with ethanol, the amount of oxidized proteins and lipids decreased with increasing incubation time, remaining significantly higher than the control [77]. Acetaldehyde, due to its highly reactive carbonyl group, interacts with many molecules in blood (hemoglobin, protein coagulation factors, etc.), forming toxic adducts with them. It is possible that the decrease in the content of protein carbonyl groups during incubation occurs due to the formation of such adducts. Another reason may be the formation of protein cross-links. Polyacrylamide gel electrophoresis revealed high-molecular-weight protein aggregates in blood samples treated with acetaldehyde; these aggregates were absent in samples with ethanol and control [77].

A decrease in LPO products during prolonged incubation of blood samples with acetaldehyde may be associated with the formation of aldehyde hybrid adducts. LPO products, particularly, malondialdehyde, easily interact with blood proteins with adduct formation; such adducts can consist of various combinations of malondialdehyde, acetaldehyde, and protein complexes that play an important role in the pathogenesis of ethanol-induced diseases [78, 79].

Analysis of peripheral markers of OS in patients with alcohol withdrawal revealed an increase in the level of protein carbonyls, LPO products [61, 80-82], and the product of oxidative modification of DNA (8-OHdG) [83, 84] in plasma samples. An increase in the carbonyl groups of proteins was also found in the erythrocyte ghosts of patients [85]. High levels of oxidative modification of macromolecules and aminotransferase activity in patients with alcohol withdrawal were also found in serum [86, 87]. The relationship between the level of oxidation (carbonylation) of blood plasma proteins and the severity of withdrawal symptoms in patients was shown [88]. Patients with alcoholic delirium with a predominance of the psychotic component had an increased content of oxidized proteins in erythrocytes and in plasma [89]. Another study has shown that patients with delirium tremens were characterized by a significant increase in LPO processes developed under conditions of the decreased activity of the antioxidant system [90].

Studying peripheral markers of OS in patients with alcohol dependence, we have found the "personal variability" of these indicators. In most patients with alcohol withdrawal admitted to medical treatment, these parameters exceeded

the normal values (OS was pronounced), and after the standard anti-alcohol treatment, they significantly decreased (i.e. OS severity decreased). At the same time, there were patients (about 20%) with basically normal levels of OS markers upon admission. During their treatment, products of oxidation of proteins and lipids increased in plasma [91]. Thus, the anti-alcohol treatment in different groups of patients with different initial oxidative status was accompanied by opposite changes in the peripheral OS markers. In the group of patients with the normal level of OS markers the anti-alcohol treatment resulted in the increase in their concentration, while in the group of patients with manifested severe OS the treatment decreased the concentration of plasma OS markers. These results indicate that the role of OS in the pathogenesis of the disease is not completely clear, and it is necessary to continue research, further collection and comparison of experimental and clinical data.

These results are consistent with the literature data on the state and severity of OS at different stages of the treatment of alcoholic disease. As a rule, high rates of oxidative modification of proteins and lipids are detected in patients with alcohol withdrawal. In most studies the anti-alcohol treatment helps to reduce the severity of OS. However, in some cases, such a decrease after anti-alcohol therapy was not found. For example, patients with alcoholic liver damage (and alcohol withdrawal) admitted to the alcohol withdrawal treatment, had high values of peripheral blood OS-markers, LPO products (conjugated dienes and Schiff bases). At the same time, after 10-15 days of basic therapy aimed at detoxification and correction of the main parameters of homeostasis, these indicators remained high, exceeding the levels found in healthy individuals by more than 2 times [92].

Personal variability in the level of peripheral OS markers in patients with alcoholism can be due to many factors, particularly, somatic burden, the stage of alcoholic disease, previous pharmacotherapy, genetic factors, etc.

OS also plays an important role in DNA damage in alcohol dependence [93, 94]. As already mentioned, the concentration of the DNA oxidation product 8-OH-2′dG in the blood plasma of alcoholic patients was higher than in healthy individuals [84, 95]. The accumulation of acetaldehyde in alcoholism due to OS development leads to the formation of an acetaldehyde-DNA adduct, N_2-ethyldeoxyguanosine, which induces DNA damage, mutations, and impaired cell proliferation [96]. A more detailed profiling of acetaldehyde and DNA adducts in DNA samples isolated from the cells of the oral cavity of volunteers taking alcohol, resulted in identification of 22 adducts. In addition to the expected N_2-ethyldeoxyguanosine, these included N_6-ethyldeoxyadenosine and N_4-ethyldeoxycytidine [97]. Acetaldehyde-induced DNA damage and mutations in hematopoietic stem cells have been described. These damages lead to DNA double-strand breaks, which, despite the recombination repair, cause significant chromosomal rearrangements [98].

CONCLUSIONS

As can be seen from the data considered in this review, a distinctive feature of OS in alcoholism is that ethanol and its metabolite acetaldehyde play an important role in its formation and development. Results of observations obtained during the study of OS in patients with alcohol dependence (low levels of peripheral OS markers in some patients, opposite directions of changes in their concentration during anti-alcohol treatment) show the need to continue research in this direction. This is especially needed in order to study the characteristics of the biological status of the body of such patients and possible protective action of the OS at a certain stage of development of alcohol dependence. Data on the protective role of OS in liver pathology are presented in a recent review [99]. They indicate that, on the one hand, OS contributes to the progression of chronic viral hepatitis and non-alcoholic fatty liver disease and the initiation of carcinogenesis, and on the other hand, OS acted as an anticancer reaction necessary for the destruction of tumor cells. The authors of this review conclude that OS may be a cancer-initiating response that should be suppressed in the precancerous stage in patients with cancer risk factors, but OS should not be suppressed in the post-cancerous stage, especially in patients taking anticancer drugs.

The paradoxical effects of OS, its role in the pathogenesis of alcohol dependence require further studies. Solving new issues that arise during clinical and experimental studies will undoubtedly be useful both in terms of new fundamental knowledge about the role of OS in the pathogenesis of alcoholism and for practical use in the search for new more effective approaches to the treatment and rehabilitation of patients with alcohol dependence.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or using animals as subjects.

CONFLICT OF INTEREST

The authors declare no conflict of interests

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ОСОБЕННОСТИ ОКИСЛИТЕЛЬНОГО СТРЕССА ПРИ АЛКОГОЛИЗМЕ

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Рассмотрены молекулярные механизмы формирования и развития окислительного стресса (ОС) у больных алкогольной зависимостью. Основное внимание уделено эффектам этанола и его метаболита ацетальдегида, связанным с дополнительными источниками генерации активных форм кислорода (АФК) при поступлении в организм экзогенного этанола. Приведены результаты собственных исследований влияния этанола и ацетальдегида на концентрацию периферических маркеров ОС — продуктов окислительной модификации белков (карбонилы белков), липидов (продукты перекисного окисления липидов), ДНК (8-гидрокси-2-дезоксигуанозин, 8-OHdG) плазмы крови *in vitro*. Проанализированы изменения этих показателей и активности антиоксидантных ферментов (СОД, каталаза) у больных алкогольной зависимостью. Приведены собственные и литературные данные, позволяющие сделать предположение, что на определённой стадии заболевания ОС может играть не патогенетическую, а защитную роль в организме.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: окислительный стресс; активные формы кислорода; периферические маркеры окислительного стресса; этанол; алкоголизм

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