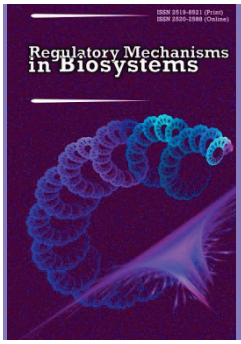

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Oxidative stress and disruption of the antioxidant defense system as triggers of diseases

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Oxidative stress is a state when the content of free radicals in a living organism is excessive. Molecules of free radical nature start a chain reaction that disrupts the integrity of cells, leading to their damage or death. The article examines the issue of intensification of oxidative stress processes and changes in the antioxidant defense system during the occurrence, development, and treatment of diseases of various etiologies. The principles of antioxidant/prooxidant balance regulation at the physiological and biochemical levels in living organisms are discussed. It was determined that the phenomenon of oxidative stress, as a completely special type of stress, is mediated by free radicals that have a destructive effect on the membranes of living cells. Free radical molecules are damaging agents for nucleic acids, proteins and lipids. The leading role in biological systems is played by oxygen free radicals, namely superoxide anion. The system of antioxidant protection, which prevents the harmful effects of oxidative stress on living organisms, is described in detail. The work describes the components of the antioxidant protection system, such as electron acceptors – vitamins E and K3; acceptors of superoxide radical anions – methionine, cysteine; scavengers of hydroxyl radicals – aliphatic alcohols; factors for detoxification of toxic products of lipid peroxidation, tocopherol, ionol, superoxide dismutase, glutathione peroxidase system, chelators of metals with variable valence (complexons) and others. According to the nature and mechanism of action, antioxidant protection agents are divided into hydrophilic and hydrophobic, enzymatic (catalase, superoxide dismutase, glutathione peroxidase system, glutathione, ascorbic acid, adrenaline, serotonin, tocopherols, retinoids, flavonoids, phospholipids, ceruloplasmin) and non-enzymatic factors. It is noted that in the human body, oxidative stress is the cause or an important component of many serious diseases, such as oncological pathologies, neurodegenerative processes (atherosclerosis and Alzheimer's disease), diseases of the gastrointestinal tract, as well as aging. Although in some cases, oxidative stress can act as a protective mechanism in the body. Thus, the human immune system uses oxidative stress to fight pathogens, and some reactive oxygen species can serve as mediators in signal transmission during the immune response. Therefore, the biochemical mechanism of the development of many diseases of different etiology is closely related to disturbances in the antioxidant defense system and the occurrence of oxidative stress.

Keywords: superoxide anion; catalase; superoxide dismutase; glutathione; ceruloplasmin; antioxidant protection.

Introduction

As a factor of the external environment, oxygen affects living organisms in two ways: on the one hand, it is absolutely necessary, and on the other hand, with molecular oxygen and its derivatives – free radicals, programmed cell death and many pathological conditions (carcinogenesis, atherosclerosis, chronic inflammation and degenerative changes) are associated. Regulation of the antioxidant/pro-antioxidant balance at the physiological level begins long before oxygen reaches the tissues. An important role is played by the partial pressure of oxygen in the blood, which is regulated by its oxygen-binding properties. The number of erythrocytes and the level of hemoglobin, as parameters of the homeostasis system, are also found to be a physiological regulator of oxygen flow to tissues and the activity of free radical processes in the body (Toboła-Wróbel et al., 2020). Oxidative modification of proteins, nucleic acids, membrane lipids in living cells with active oxygen metabolism occurs tens of thousands of times every day. But the vast majority of these modifications do not have consequences for the normal vital activity of the body and reflect the ability of the protective antioxidant system (AOS) in the cells and outside them (blood and secretions) (Vassalle et al., 2020). This system includes enzymes (superoxide dismutase, catalase, peroxidase, selenium-containing glutathione peroxidases, etc.), low molecular weight compounds that catalyze free radical reactions or trap oxidation products (proteins and peptides, glutathione, uric acid, amino acids, vitamins E, C, P, carotenoids, phenolic compounds, trace elements). The preventive effect of the use of antioxidant vitamins, trace elements and many amino acids in various animal and human diseases has long been proven.

Oxidative stress

Oxidative stress may lead to the cell damage as a result of lipid, carbohydrate, and protein oxidation. Oxidative stress is a completely special type of stress mediated by free radicals that have a destructive effect on cell membranes (Chang et al., 2020). Free radicals are extremely unstable molecules with an unpaired electron in the outer orbit, which very easily enter into chemical reactions. Colliding with other molecules, they take away an electron from them, as a result of which molecules without such electrons, in turn, become free radicals, and - in a very short time, the most dangerous chain reaction for the body develops, which leads to damage to proteins, nucleic acids (DNA) and membrane lipids. The result of this destructive action is oxidative stress. It provokes inflammatory processes and contributes to the development of bronchial asthma, diabetes, arthritis, heart and cancer diseases (Grzesik et al., 2019; Erdem et al., 2021).

Free radicals

The nucleus of an atom is surrounded by electron orbitals, each of which contains a maximum of two electrons with different spin quantum

numbers. A hydrogen atom has one outer orbital, nitrogen, carbon and oxygen atoms each have 4 outer orbitals. Free radicals are highly active molecules or atoms with unpaired electrons that have electrons in the outer orbital that are not involved in the formation of a chemical bond (Moller et al., 2023). Atoms or small molecules that are free radicals are more unstable than large atoms and molecules because the latter can capture an electron to form a resonance structure (i.e., a stable structure) (Khadem et al., 2015).

Free radicals can damage nucleic acids, proteins and lipids (Khedr et al., 2019). For biological systems, oxygen free radicals are most important, in particular, superoxide-anion ($.O^{2-}$), nitric oxide (.NO) and hydroxyl radical (.OH) (Fig. 1). Nitric oxide is a relatively inactive radical that lives for only a few seconds and quickly reacts with oxygen (Zych et al., 2023).

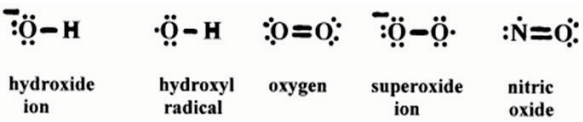

Fig. 1. Free radicals

The nitric oxide radical interacts with the superoxide anion, then peroxynitrite ($ONOO^-$) is formed, which decomposes with the formation of a hydroxyl radical. Peroxynitrite, like the hydroxyl radical, reacts directly with proteins and other macromolecules with the formation of aldehydes and ketones, cross-linking and products of lipid peroxidation. Only 1–4% of DNA single-strand breaks are provoked by peroxynitrite and the hydroxyl radical. In addition, hydrogen peroxide (H_2O_2) and hypochlorite (OCl^-) are not free radicals by themselves, but these oxygen-containing molecules can facilitate the formation of free radicals. All these oxygen-containing molecules are united by the term reactive oxygen species (ROS). ROS act on bases in nucleic acids, amino acids of protein side chains, and double bonds in unsaturated fatty acids. Damage to macromolecules (and the cell as a whole) as a result of the action of ROS is called oxidative stress.

Free radicals are unstable and extremely reactive. They gain stability by receiving electrons from nucleic acids, lipids, proteins, carbohydrates, or other molecules that may be nearby and cause subsequent chain reactions that result in cellular damage or disease (Vassalle et al., 2020). There are two main types of free radical derivatives: reactive oxygen derivatives (RODs) and reactive nitrogen derivatives (RNDs).

There are three main types of RODs: superoxide (O2•-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH•). The superoxide radical is formed due to the leakage of electrons from the electrotransport chain (ETC). Dismutation of superoxide is the result of the formation of hydrogen peroxide. OH• is highly reactive and can transform purines and pyrimidines, which in turn leads to DNA damage. Some oxidase enzymes can directly form hydrogen peroxide radicals. RODs causesmore than 100 diseases. They play a physiological and pathological role in the field of female reproductive organs. Numerous experiments on animals and humans have proven the presence of RODs in the area of female reproductive organs: ovaries, fallopian tubes, embryos (Toboła-Wróbel et al., 2020).

Nitric oxide (NO) is synthesized during the enzymatic conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS). Nitric oxide strongly relaxes arteries and veins in smooth muscles and, to a lesser extent, inhibits aggregation and adhesion (clumping) of platelets. Nitric oxide as a donor performs a vasodilating function, and therefore can be used in therapeutic measures. Nitric oxide acts on a variety of tissues, regulating a number of physiological processes, but in excess can be toxic. Reactive nitrogen derivatives are associated with asthma, coronary disease, septic shock and atherosclerosis. Two common examples of reactive nitrogen derivatives are nitric oxide (NO) and nitrogen dioxide. NO-produces the NO-synthase enzyme. There are three types of NO-synthase (NOS) isozymes in mammals including endothelial NO-synthase, neuronal NO-synthase, and inducible NO-synthase (Kashyap et al., 2023).

Oxidation of lipids by molecular oxygen is a chain free radical reaction called lipid peroxidation (LPO) (Sosa et al., 2013). It goes through several stages called initiation, continuation, branching and breaking of the chain. The initiation of the chain reaction begins with the penetration of the free radical into the lipid bilayer of membranes and lipoproteins. At the same time, lipid radicals are formed (Zych et al., 2023). The lipid radical (L•) reacts with molecular oxygen dissolved in the medium; at the same time, a new free radical is formed – the lipoperoxide radical (LOO•). This radical attacks one of the neighboring phospholipid molecules with the formation of lipid hydroperoxide LOOH and a new radical L•. The alternation of the last two reactions is a chain reaction of lipid peroxidation. Significant acceleration of lipid peroxidation is observed in the presence of small amounts of divalent iron ions. The peroxide radical can also form a lipid endoperoxide radical, the breakdown of which leads to the formation of a number of products, including malondialdehyde. In biomembranes, chains can consist of a dozen or more links. But in the rest, the chain of reactions is interrupted as a result of the interaction of free radicals with antioxidants (InH), metal ions of variable valence (for example, the same iron ions Fe^{2+}) or with each other.

System of antioxidant protection

Antioxidants are compounds that prevent the formation of reactive oxygen species and thereby prevent the corresponding pathological effects on body structures (Minnelli et al., 2020). Antioxidants are various water-soluble and hydrophobic compounds, the action of which ultimately inhibits the formation of reactive oxygen species and reduces the concentration of the products of reactions that occur with their participation (Naparło et al., 2020). Most of the components of the antioxidant defense system (ADS) are characterized by the specificity of their impact on various links in the formation of reactive oxygen species and free radical oxidation (Al-Taher et al., 2020). Enzymes that specifically eliminate reactive forms of oxygen and intermediate products of lipid peroxidation (LPO) are known (catalase, Cu, Zn, Mn-containing superoxide dismutases, glutathione peroxidase system).

The components of the antioxidant protection system are considered to be: electron acceptors – vitamins E and K_3; acceptors of superoxide radical anions – methionine, cysteine; scavengers of hydroxyl radicals – aliphatic alcohols; factors of elimination of toxic products of LPO tocopherol (TF), ionol, superoxide dismutase, glutathione peroxidase system; metal chelators with variable valence (complexons). Components of antioxidant protection are divided into hydrophilic and hydrophobic, enzymatic (catalase, superoxide dismutase, glutathione peroxidase system, glutathione, ascorbic acid, adrenaline, serotonin, tocopherols, retinoids, flavonoids, phospholipids, ceruloplasmin) and non-enzymatic (Kashyap et al., 2023).

Superoxide dismutase

Superoxide dismutase (SOD) – peroxide: peroxide oxidoreductase EC 1.15.1.1 catalyzes the reaction between two superoxide – anions, as a result of which hydrogen peroxide and triplet oxygen (oxygen in the ground state) are formed:

$$O_2^{\bullet-} + O_2^{\bullet-} + 2H^+ \rightarrow O_2 + H_2O_2$$

As a result, hydrogen peroxide is formed, capable of inactivating superoxide dismutase (Reddy, 2022). That is why superoxide dismutase is localized and usually functions in cooperation with catalase, which quickly and efficiently decomposes hydrogen peroxide H_2O_2. The active center of the superoxide dismutase enzyme contains metal atoms with variable valence. As early as 1939, Mann and Keilin isolated a copper-containing protein from bull erythrocytes, which they named hemocuprein; then this protein began to be called erythrocuprein. Later, similar proteins were isolated from other tissues (hematocuprein, cerebrocuprein), and it was found that all of them, along with copper (Cu), also contain zinc (Zn). In the work of McCord and Frydovych in 1968, it was shown that Cu, Zn-containing protein is an enzyme that catalyzes the dismutation reaction of superoxide radicals. Also, it was established that organisms of various degrees of complexity, which utilize oxygen in metabolic processes, contain enzymes with SOD activity. Enzymes differ in their primary structure and the nature of the metals included in the active site (Bocca et al., 2017).

Cu, Zn-SOD can be considered as a eukaryotic cytosolic enzyme, Fe-SOD and Mn-SOD as prokaryotic enzymes, but Mn-SOD is contained in the mitochondrial matrix of eukaryotes; Cu, Zn-SOD was detected in a number of bacteria, and Fe-SOD was found in some plants. Superoxide

dismutases are mainly intracellular enzymes and only a small part of the activity was detected by Marklund et al. (2001) in the extracellular fluids of mammals in the form of glycosylated Cu, Zn-SOD tetrameter. In the matrix of mitochondria, radicals originating from the electrotransport chain, manganese-containing SOD (Mn-SOD) are present and dismutate; increasing the amount of $O2^{\bullet-}$ stimulates the synthesis of Mn-SOD (Erdem et al., 2021). Fe-SOD is also found in bacteria. The most widespread form of superoxide dismutase is Cu, Zn-SOD, which is contained in the cytosol of cells and the intermembrane space of mitochondria. SOD is one of the very stable enzymes.

Thus, Mn-SOD and Cu, Zn-SOD are the most important antioxidant enzymes that inactivate the superoxide radical and, accordingly, reduce the overall toxic effect of oxygen and its active forms. Superoxide dismutase is the most widespread antioxidant factor in the animal body. Its content in the cell depends on the level of metabolic activity.

At present, much attention is paid to the study of changes in the activity of erythrocyte SOD in the process of aging of organisms and in some diseases, such as hemolytic anemia, ischemia, and a number of neurological diseases. Superoxide radicals play a significant role in the development of inflammatory processes. The result of these studies was the use of SOD as an anti-inflammatory agent (orgothein, peroxynorm). Orgotein is used clinically for the treatment of inflammatory processes, osteoarthritis, bursitis, practicitis, and cystitis. Successful treatment of inflammatory processes with superoxide dismutase allows this enzyme to be considered as an alternative to corticosteroids.

Catalase

Hydrogen peroxide catalase: hydrogen peroxide oxidoreductase, EC 1.11.1.6 is a hemoprotein that decomposes hydrogen peroxide into water and free oxygen. Catalases are localized in peroxisomes, which degrade toxic substances (phenols, formic acid, formaldehyde, and ethanol) using peroxide.

$$H_2O_2 + H_2O_2 \rightarrow O_2 + 2H_2O$$

The reaction takes place in two stages: first, an enzyme complex is formed with the first molecule of hydrogen peroxide, then with the second molecule of hydrogen peroxide. That is, antioxidant enzymes: SOD and catalase, functioning together, in most cases inactivate in good time reactive oxygen species (ROS), $O_2\bullet$ and H_2O_2, which are formed both in the process of normal cellular activity and in conditions of significant activation of lipid peroxidation, including pathologically determined. But the most effective lipid peroxidation is activated in the lipid (phospholipid) structures of biomembranes and is accompanied by the formation of lipid peroxides, which are not sufficiently neutralized by the SOD-catalase system (Mohamed et al., 2020). In addition, even in conditions of successful deactivation of superoxide (SOD) and hydrogen peroxide (catalase) there is a danger of the formation of a particularly highly reactive radical OH•, at least according to the Haber-Weiss reaction:

$$O_2^{\bullet-} + H_2O_2 \xrightarrow{Fe^{2+}} OH^{\bullet} + O_2 + OH^-$$

The lifetime of the $OH^{\bullet}$ radical is so short that its enzymatic inactivation is obviously impossible; other protection mechanisms are required. It is clear that the more completely SOD and catalase inactivate their active substrates, the less is the possibility of $OH^{\bullet}$ radical formation (Zuo et al., 2022).

The glutathione system

The glutathione-dependent antioxidant system includes three glutathione-dependent enzymes: glutathione peroxidase (GPO), glutathione reductase (GR) and glutathione transferase (GT).

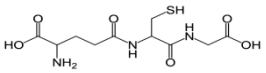

Fig. 2. The structure of glutathione

The main metabolite of the system is tripeptide glutathione (GSH) – glutamylcysteinylglycine (Fig. 2) (Menshikov, 2006), which also has its own antioxidant activity, functions as a cofactor, hydrogen donor, metabolite and substrate with enzymes of the system, as well as with SOD and catalase (Farhat et al., 2018). From the point of view of the molecular mechanism of functioning in the glutathione antioxidant system, four links can be distinguished:

1) ensuring the functioning of the system – glutathione reductase;

2) detoxification of peroxide compounds – glutathione peroxidase and catalase;

3) antiradical protection – superoxide dismutase and reduced glutathione;

4) detoxification of electrophilic compounds – glutathione transferase.

Enzyme glutathione reductase (GR) – NAD(F)H: oxidized glutathione oxidoreductase, EC 1.6.4.2 (Zhang et al., 2017), catalyzes the following reaction:

$$2NAD(F)H + GS\text{-}SG \rightarrow 2NAD(F) + 2GSH$$

The central and important position of this enzyme in the metabolism of glutathione and its entire system is due to the fact that it carries out the only known mechanism of reduction of glutathione to GSH from its oxidized form GS-SG. Other enzymes besides glutathione synthetases are consumers of reduced glutathione (Zhang et al., 2017). The glutathione reductase enzyme is a flavonoid protein with a flavinadenine dinucleotide prosthetic group; its molecule consists of two identical subunits. GR is a classic cytosolic enzyme of all eukaryotic cells. Molecular weight from 100 kDa (liver) to 300 kDa (vitreous body). The enzyme glutathione peroxidase (GPO) – glutathione: hydrogen peroxide oxidoreductase, EC 1.11.1.9) is one of the most important components of the cell's antiperoxide enzyme system (Erdem et al., 2021). This enzyme functions mainly in the cytoplasm of the cell. The enzyme molecule contains selenium atoms, which largely explains its antioxidant properties. Inactivation of hydrogen peroxide and organic hydroperoxides (in particular, proteins, nucleic acids) by glutathione peroxidase occurs in the following reactions:

$$2GSH + H_2O_2 \rightarrow G\text{-}SS\text{-}G + 2H_2O,$$

$$2GSH + ROOH \rightarrow G\text{-}SS\text{-}G + ROH + H_2O.$$

GPO is a selenoprotein, but it is possible that GPO is present as a selenoglycoprotein in human blood serum. The GPO molecule has a molecular weight close to 74 kDa and consists of four identical subunits. GPO neutralizes not only H_2O_2 hydrogen peroxide, but also organic peroxides, including lipid peroxides, which are formed in the body during the activation of lipid peroxidation (Menshikov, 2006). The enzyme is localized mainly in the cytosol of cells, a small amount is also found in microsomes. This enzyme functions together with GR, protecting cells from hydrogen peroxide generated outside of them. Although the contribution of catalase and glutathione peroxidase in the reduction of H_2O_2 in the liver is approximately the same, the role of glutathione peroxidase is much more important for the cell as a whole. This is argued by the following facts: 1) catalase is concentrated mainly in peroxisomes, and glutathione peroxidase neutralizes H_2O_2 in the cytosol and mitochondria; 2) the affinity of glutathione peroxidase to H_2O_2 is higher, therefore it protects against the more frequently occurring low concentrations of H_2O_2; 3) deficiency or inhibition of glutathione peroxidase (but not catalase) leads to increased peroxidation and damage to some cells; 4) catalase is absent in some tissues (heart), and then glutathione peroxidase plays a major role in gross H_2O_2 metabolism. Recovery of H_2O_2 not only removes this active substance, but also prevents the appearance of organic hydroperoxides. Glutathione peroxidase not only prevents the accumulation of hydroperoxides (ROOH), but also effectively restores them. Glutathione transferases work in the same way, but they do not reduce H_2O_2. The joint work of these enzymes prevents the further progression of peroxidation, the spread of non-enzymatic reactions, and the accumulation of secondary metabolites (Khedr et al., 2019). GSH, glutathione peroxidase and glutathione transferase inhibit lipid peroxidation in microsomes. These enzymes restore peroxidation products of free nucleotides and DNA (at the same time, glutathione transferase is part of chromatin and plays the role of a DNA repair enzyme); in the total glutathione peroxidase activity in the cytosol, glutathione peroxidase is of primary importance (68%), and glutathione transferase (86%) in the nuclei.

Glutathione transferase

Glutathione transferase (GT) is a family of multifunctional proteins – enzymes that use reduced glutathione for conjugation with hydrophobic

substances, their reduction or isomerization. There are many isozymes, and a complete gene structure has been established for one of them. GTs protect cells from xenobiotics and perform important functions in endogenous metabolism. GTs in the living world are universal, in the cell they are found mainly in the cytosol. GT activity is regulated by metabolites, sex hormones, catecholamines, cAMP; glutathione transferases in their synthesis are also induced by many substances. In some cases, malignant growth is accompanied by an increase in the activity of GT, especially some isoenzymes, which allows them to be used as markers of some tumors. Determination of GT in human blood plasma is of certain importance in clinical practice, because the activity of GT in plasma increases with a number of poisonings and liver diseases. In general, the medical aspects of the problem are not sufficiently studied (Reddy, 2022).

Glutathione transferases (GT; EC 2.5.18) were identified in 1961. Now works on GT are published in a huge number. GT is of significant interest as a vivid example of multifunctional polyisoenzyme proteins. In recent years, significant progress has been achieved in virtually all areas of GT research, which is based on the general development of enzymology. GT is an organ-specific general oncological marker. Determination of GT in blood serum allows diagnosis not only of malignant lesions of the lungs, but also pathological processes associated with an increased risk of malignant transformation, as well as monitoring the effectiveness of surgical treatment. The absence of a tendency to decrease the level of the marker to normal values within three weeks indicates insufficient effectiveness of the treatment and possible further generalization of the tumor process.

The huge number of reactions carried out by GT can be divided into four main types.

1. Attachment of a complete molecule of reduced glutathione (GSH) to the substrate (R):

$$R + GSN \rightarrow HRSG$$

2. Nucleophilic substitution:

$$PX + GSH \rightarrow RSG + HX,$$

where the initial group is represented by X^-, Hal^-, NO_2^-, HSO_4^-, RO^-, RS^-, SI^- and others.

3. Reduction of organic peroxides to alcohols:

$$ROOH + 2GSH \rightarrow ROH + GSSG + H_2O$$

4. Isomerization (steroids, prostaglandins) (Yang et al., 2020).

Non-enzymatic system of antioxidant protection

Non-enzymatic antioxidants are also known as synthetic antioxidants or dietary supplements. The antioxidant system affects the absorption of antioxidant vitamins or minerals such as vitamin C, vitamin E, selenium, zinc, taurine, hypotaurine, glutathione, beta-carotene, and carotene (Yang et al., 2020). Vitamin C is a chain of antioxidants that stop the reproduction of the peroxide process. Vitamin C also helps to reactivate oxidized vitamin E and glutathione. Taurine, hypotaurine and transferrin are mainly embedded in the tubes and follicular fluid, where they protect the embryo from oxidative stress. Glutathione is present in the oocyte and tubal fluid and plays a role in improving the development of the zygote up to the blastocyst stage. About 95% of all oxygen consumed by the cell is restored in the mitochondria to water in the process of oxidative phosphorylation. Five percent of oxygen is converted into ROS as a result of biochemical reactions (usually enzymatic). This amount of radicals can cause enormous damage to the cell. Enzymes: superoxide dismutase, catalase and glutathione peroxidase, as well as some low-molecular antioxidants – vitamin C, uric acid, glutathione (Fig. 2) work to neutralize ROS in the cell. Other antioxidants are also present in living cells.

Ceruloplasmin is a multifunctional glycoprotein, a metalloenzyme that contains 98% of copper in the blood. Its functions in the body are as follows: ceruloplasmin carries out the transport of copper, which is necessary for the enzymes of tissue respiration, it is necessary for normal hematopoiesis, especially for the synthesis of hemoglobin. Ceruloplasmin is an active antioxidant, it inhibits and prevents the appearance of harmful underoxidized products that are formed in large quantities in many diseases, including oncological pathologies. The functions of ceruloplasmin are very diverse. The English biochemist D. Curzon discovered that this enzyme catalyzes the oxidation of divalent iron ions into trivalent iron, which is an excellent oxidant in cytochromes. Moreover, ceruloplasmin not only participates in the synthesis of hemoglobin, but also contributes to the formation of transferrin (Reddy, 2022). In 1944, ceruloplasmin (CP) was first described by Swedish scientists Holmberg and Laurell and characterized in detail a few years later. Even then, it got its name, which means "heavenly blue plasma protein". At the end of the 1970s, the first reports appeared about the ability of CP to play the role of scavenger of superoxide anion radicals ($O_2^{\bullet}$) (Menshikov, 2006). At the same time, the action of the enzyme, as it turned out, does not depend on its interaction with substances previously reduced by $O_2^{\bullet}$, but most likely depends on the interaction with $O_2^{\bullet}$ itself, which is similar in a number of parameters to the action of superoxide dismutase. Later, Bannister et al. (1968) concluded that they had observed in experiments the usual pattern of oxidation of O_2 by enzyme-oxidase (CP), which is described by the following equation:

$$4O_2 + 4H^+ + O_2 \rightarrow 4\,O_2 + 2H_2O$$

The true dismutation reaction catalyzed by superoxide dismutase differs in that more oxygen is added and the equation takes the following form:

$$3O_2^{\bullet} + 4H^+ + 2O_2 \rightarrow 3O_2 + 2H_2O_2$$

Also, CP prevents the accumulation and action of toxic oxidizing radicals in blood plasma due to ferroxidase activity:

$$4Cu\,(II) + 4Fe^{2+} \rightarrow 4Cu(I) + 4Fe^{3+};$$

$$4Cu(I) + O_2 + 4H^+ \rightarrow 4Cu(II) + 2H_2O$$

By catalyzing the oxidation of Fe^{2+} to Fe^{3+}, the enzyme maintains a Fe^{2+}:O_2 ratio of 4:1, allowing the transfer to O_2 to form water and preventing the non-enzymatic reaction that produces oxygen:

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2^{\bullet}$$

By oxidizing Fe^{2+} to Fe^{3+}, ceruloplasmin can prevent the Fenton reaction: the formation of OH radicals during the interaction of Fe^{2+} with H_2O_2:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^{\bullet}$$

Promoting the incorporation of oxidized Fe^{3+} into ferritin, ceruloplasmin inhibits superoxide and ferritin-dependent lipid peroxidation (LPO). It has also been shown that ceruloplasmin can act as a growth factor due to its antioxidant properties (Zhang et al., 2017). A decrease in the level of ceruloplasmin is noted in Wilson-Konovalov disease and Menkes disease. Next, after cytochrome-C-oxidase and AO-enzymes, the third line of defense of cells is formed by substances – antioxidants, which have anti-radical and anti-peroxide activities. They are present where there are substrates – targets for the attack of free radicals and peroxides, biological structures most vulnerable to the LPO process (Menshikov, 2006). Such structures primarily include biological membranes, and the most adequate targets in them are polyunsaturated (polyene) fatty acids – linoleic (2 double bonds), linolenic (3 double bonds), arachidonic (4 double bonds).

That is why fat-soluble antioxidants are embedded directly in the structure of plasmatic, mitochondrial, microsomal, lysosomal membranes, karyolem. These are tocopherols (vitamin E) (Fig. 3), ubiquinones (plastoquinones in plants), carotenoids, vitamin A preparations (primarily retinal).

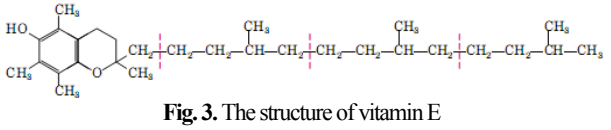

Fig. 3. The structure of vitamin E

From the group of fat-soluble antioxidant-membranoprotectors, the most important role is played by α-tocopherol. The concept of antioxidant-mechanism of biological action of tocopherol was first formulated by A. L. Tappel in 1953, although its antioxidant-properties were known much earlier. The tocopherol molecule consists of a benzene nucleus with a hydroxyl group performing the antioxidant function, and a phytol side chain that interacts the tocopherol molecule with membrane structures. Thus, the reaction takes place, in particular, with the hydrocarbon chain of arachidonic acid, and this can increase the effectiveness of antioxidant protection of membranes. α-Tocopherol is not synthesized in the body of humans and mammals, it belongs to the necessary nutritional factors – vitamins. Vitamin E, along with other antioxidant vitamins, plays the role of a natural immunoregulator, has a pronounced hepatoprotective effect.

Thus, α-tocopherol is one of the most important universal fat-soluble antioxidants with membrane-protective, antimutagenic activity; interacting with natural antioxidants of other classes, it is the most important regulator

of the oxidizing homeostasis of cells and organisms, the most important component of the antioxidant system of tissues.

Ubiquinone or coenzyme Q, similar to α-tocopherol, is a fat-soluble compound and has antioxidant activity, forming a redox buffer system ubiquinol – ubiquinone (Fig. 4). Its most important biological role is associated with participation in the mitochondrial electron transport chain as one of the components and a coenzyme that is part of this chain: succinate-NADH-Q-reductase and cytochrome-C-Q-oxidase systems (Reddy, 2022).

The role of ubiquinone as the most important carrier of electrons in the respiratory chain determines its behavior as a regulator of pro-oxidant-antioxidant homeostasis and its effectiveness in various diseases: myocardial ischemia, hypertension, anemia. Ubiquinone, similar to α-tocopherol, is a weak antioxidant, but, like it, it stimulates an increase in the level of natural antioxidants in the body.

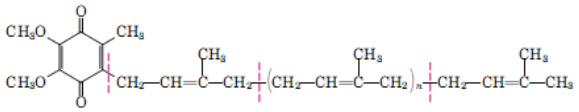

Fig. 4. Structure of ubiquinone

Vitamin A or retinol, retinal, retinoic acid and its provitamins – β-carotene and other carotenoids (Fig. 5) stimulate the body's growth in childhood (mainly carried out by retinoic acid), take part in photoreception (retinal), stimulation of reproduction, work immune system, increase in barrier properties and differentiation of the epithelium.

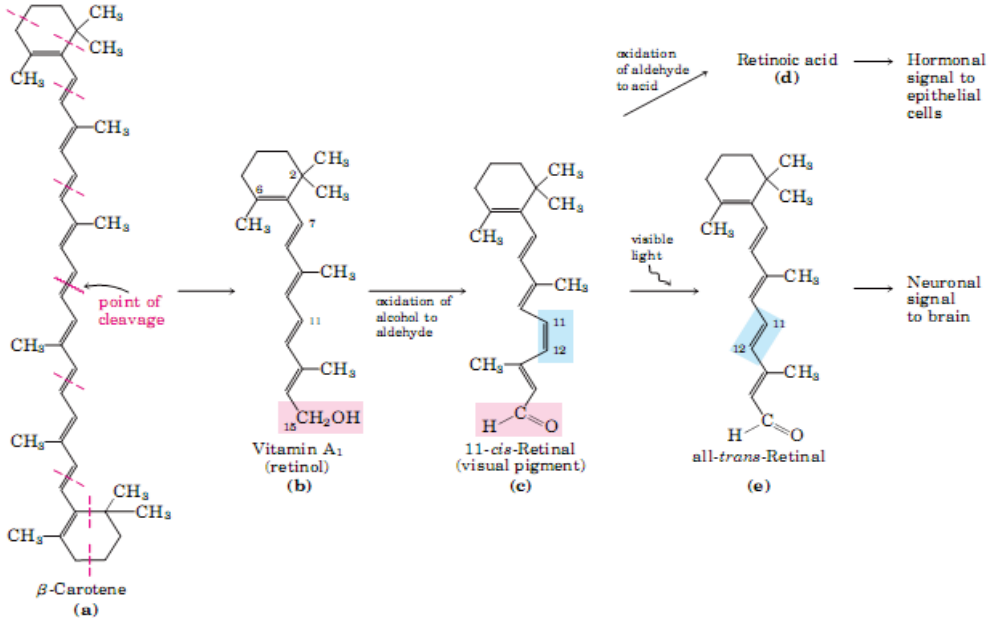

Fig. 5. Vitamin A and its precursors and derivatives: *a* – β-carotene; *b* – vitamin A (retinol); *c* – 11-cis-retinal; *d* – retinoic acid; *f* – trans-retinal

The membrane-stabilizing effect of retinoids consists in their regulatory effect on microsomal oxidation, as well as to a large extent the effect on chromatin, cell proliferation, biosynthetic processes associated with antioxidant activity. Vitamin A and carotenoids also have antitoxic, antiradiation, anticarcinogenic, antimutagenic, geroprotective effects (Moller et al., 2023). Metal ions with variable valence belong to the group of biotic macro- and microelements, which are part of many enzymatic systems, perform, in particular, a catalytic role in the active centers of oxidoreductases, directly participate in the implementation of most redox reactions. Free metal ions present in biological fluids act as cofactors of many enzyme systems, contributing to the catalysis of metabolic reactions. But metal ions Cu^{+}, Cu^{2+}, Fe^{2+}, Fe^{3+}, as well as ions Mg^{2+}, Mn^{2+}, Co^{2+} are able to catalyze non-enzymatic oxidation reactions, accelerating the oxidation of substrates. The addition of Fe^{2+} to the biological fluid or reaction mixture stimulates the LPO process. Such elements as zinc, molybdenum, and especially selenium, under similar conditions, act mainly as antioxidants, acting as factors that restrain the development of free radical oxidation.

Selenium is an analogue of sulfur, but it is more active and displaces sulfur from biologically active compounds. SeH-groups have higher electron-donating (i.e., AO) activity than SH-groups due to lower ionization potential and lower binding energy. Due to the high electron-donating activity, SeH-compounds effectively deactivate free radicals, peroxides and carcinogens. The element selenium and its preparations have a therapeutic effect in any diseases and pathological conditions accompanied by the activation of LPO process.

Consequences of oxidative stress

In humans, oxidative stress is a cause or an important component of many serious diseases, such as atherosclerosis and Alzheimer's disease, as well as aging. However, in some cases, oxidative stress acts as a protective mechanism in the body. The human immune system uses oxidative stress to fight pathogens, and some reactive oxygen species can mediate signaling (Sosa et al., 2013).

Oncological diseases

As well known, cancer represents an evolutionary process through which growing malignant populations genetically diversify. From this point of view, every factor that interacts with DNA and modifies it is a carcinogen. Therefore, ROS have a mutagenic, carcinogenic effect. One of the most studied damage markers at present is 8-oxoguanine (8-oxoGua). Its presence in DNA leads to GC-TA substitutions if not repaired prior to replication. For example, when studying the level of 8-oxoguanine in uterine myoma cells, it was found that this level correlates with the size of the tumor. The increasing level of modified bases causes instability of the genome and increases the potential for metastasis in the formed tumor. This has been shown in studies on some types of adenocarcinoma. Oxidative damage is explained by the existence of many different mutations in one carcinoma cell, with the development of the tumor, the number of these mutations increases. It is reasonable to assume that they arise in the process of tumor development. Intracellular processes play a role here (oxidative phosphorylation, fatty acid metabolism in peroxisomes, reactions involving cytochrome P_{450}, "respiratory explosion" in phagocytes), which are the main sources of free radicals that cause base changes, and therefore mutations that lead to oncological pathologies (Nowak et al., 2022).

Atherosclerosis

Atherosclerosis is a chronic disease associated with widespread damage to arteries, manifested in damage to the inner wall of arteries, depo-

sition of lipids (fatty substances, cholesterol), calcium salts and other components in it, with subsequent narrowing of the vessel lumen. With atherosclerosis, aggregates of lipids and cells are formed on the walls of blood vessels, forming peculiar plaques from the so-called "foam cells". This leads to the proliferation of cells, a decrease in the thickness of blood vessels, the deposition of calcium, etc. (Chang et al., 2020). As a result, the vessel walls become thin and fragile, and their lumens narrow. It has been reliably established that the oxidation of macromolecules is closely related to the development of atherosclerosis. About 30% of cholesterol linoleate deposited in plaques is in an oxidized state.

Most of the accumulated lipids are formed from low-density lipoproteins. At the same time, the modification of their protein apoform by aldehydes and lipid oxidation is considered a key point in the formation of plaques in atherosclerosis. Apoprotein can be easily oxidized and fragmented under the action of radiolysis or oxidation catalyzed by metal ions. Compared with the apoform, the content of 3-nitrotyrosine was found to be higher in the proteins of *in vivo* plaques. Products of protein oxidation by hypochlorous acid were also found here (Vassalle et al., 2020). Again, it is unclear which is the first, and which is the second - free radical oxidation of proteins and lipids or the formation of atherosclerotic plaques, but the participation of activated forms in this pathology is beyond doubt.

Neurodegenerative diseases

A special group of age-related neurodegenerative diseases includes Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Parkinson's disease is a degenerative disease of the nervous system characterized by involuntary tremors and reduced muscle strength. At the same time, the mind and intellect do not suffer. The disease usually occurs in middle age and gradually progresses with age. This disorder is characterized by an increased content of iron in the substantia nigra parscompacta of the brain.

It is believed that the root cause of these disorders is oxidative stress, which is accompanied by the intensification of lipid peroxidation (Zych et al., 2023). During aging, the content of protein carbonyls in human tissues increases. In the brain, the degree of increase in the content of protein carbonyls depends on the department being studied. The increase in the content of protein carbonyls with age is associated with a decrease in the activity of enzymes sensitive to ROS, glutamine synthetase and creatine kinase. Currently, the ways of ROS generation in Parkinson's disease have been clarified. Such processes involve metal ions with a change in valency (primarily iron), disruption of the electro-transport chain, end products of glycosylation, reactive microglia, and β-amyloid (Zhang et al., 2017). It is the latter as a prooxidant that is now assigned a leading role in the development of this pathology. Amyloid peptides, consisting of 39–43 amino acid residues, are formed from a precursor – a transmembrane glycoprotein. In solution, amyloid peptides aggregate into structures with a molecular weight above 15 kDa, and after that they begin to exhibit neurotoxicity. This complex, among other things, disrupts the homeostasis of calcium ions, leads to their accumulation in the cell and, apparently, is also involved in the accumulation of iron ions. Accumulation of oxidized proteins (both cytosolic and membrane) is also another indicator of induced oxidative stress in Alzheimer's disease.

Diseases of the gastrointestinal tract

The processes of peroxidation of lipids-antioxidant protection occupy a leading place in the pathogenesis of many conditions, including diseases of the gastrointestinal tract. Lipid peroxidation process – oxidative degradation of lipids, which occurs mainly under the influence of free radicals and is one of the main consequences of radioactive irradiation.

Non-specific ulcerative colitis (NSUC) is a chronic, idiopathic inflammatory disease of the mucous membrane of the large intestine, characterized by a progressive course and the possible development of complications. Among the causes of chronic inflammatory bowel diseases are infectious agents, overeating, ionizing radiation, toxic substances, drugs (salicylates, corticosteroids, immunosuppressants), tuberculosis, malignant neoplasms, hypoxia, the condition after gastric resection. Also, in general, nonspecific ulcerative colitis is primarily an inflammatory disease of the large intestine of a chronic type, characterized by the appearance of ulcers on the intestinal mucosa. Most often, NSUC is localized in the lower parts of the large intestine, namely in the rectum and sigmoid colon. Non-specific ulcerative colitis is a chronic recurrent disease of the large intestine, which is characterized by severe diffuse ulcerative-inflammatory lesions of its mucous membrane. It is known that during the development of the disease, a high activity of ceruloplasmin was observed in non-specific ulcerative colitis, which was 1.4 times higher than the control values in comparison with a group of clinically healthy individuals. Also, among patients with non-specific ulcerative colitis with anemia, the majority of patients had elevated values of this indicator. An increase in the activity of ceruloplasmin indicated the activation of the body's antioxidant protection. At the same time, an increase in the activity of superoxide dismutase was registered only in patients with nonspecific ulcerative colitis with anemia, which indicated an increase in the level of lipid peroxidation in these patients. Therefore, the existence of a close connection between the lipid peroxidation-antioxidant protection system and ferrokinetics in patients with gastroenterological pathologies is confirmed (Gorelaya, 2022).

Recently, the problems of mycotic complications in patients with pathology of the digestive organs are also becoming more and more relevant. Most often, the causative agents of mycoses caused by opportunistic yeast-like fungi are representatives of the genus *Candida* (90–93%), which can cause not only superficial lesions of the skin and mucous membranes, but also deep, systemic lesions of various tissues and organs. Candidiasis is the most common opportunistic infection among the population and accounts for 63% of the population. The increase in the incidence of candidiasis, infection and superinfection with fungi contribute to the transition of acute processes into chronic ones, the occurrence of relapses and a more severe course of the disease (Enoch et al., 2006). Recent studies have proven that the activation of lipid peroxidation, which occurs mainly in biological membranes and is an example of free radical processes in the body, is important in the pathogenesis of fungal infections. Currently, there is no doubt that the processes of free radical oxidation play an extremely important role in the vital activity of cells. When the regulation mechanisms of lipid peroxidation processes are disturbed, there is an excessive accumulation of free radicals, which lead to damage and death of the integumentary pit epithelium, suppression of the resistance of the mucous membrane of the gastrointestinal tract, and depletion of the antioxidant defense system (Dryndak et al., 2011). It was shown that in all patients there was a probable decrease in the total antioxidant activity of blood serum compared to the control: in the group without candidiasis by 15.0%, in the I group by 20.1% and in the II group by 14.1%, which indicates a possible depletion of the antioxidant defense system. In patients with gastroenterological pathology of the upper part of the gastrointestinal tract without candidiasis, the indicator of total antioxidant activity decreased by 15.0% to ($37.1 \pm 2.1\%$, $P < 0.05$), in patients of the I and II groups by 20.1% to ($34.9 \pm 1.6\%$, $P < 0.001$) and by 14.1% ($37.6 \pm 2.3\%$, $P < 0.05$), respectively. Suppression of the total antioxidant activity of blood serum in all groups of patients may indicate exhaustion of the antioxidant protection system, which is not able to neutralize the excess production of cytotoxic lipid peroxides. Such data indicate a high interest in studies of lipid peroxidation, as a mechanism that plays a major role in the pathogenesis of many fungal infections, including candidiasis.

Conclusion

Therefore, according to the data of a number of studies, it was demonstrated that oxidative stress is one of the mechanisms leading to biochemical changes that cause cytogenetic changes. Data obtained from the analysis of literature sources indicate a cause-and-effect relationship between the long-term accumulation of highly active forms of oxygen (superoxide anion radicals, hydroperoxides, hydroxyl radicals) in the cells of the body with damage to the genome (DNA mutations, single- and double-strand breaks, chromosomal aberrations, deletions, translocations), the development of inflammatory processes, metabolic disorders. A key role in this is played by a decrease in the general antioxidant activity of the blood, as well as enzymes of superoxide dismutase, catalase, and enzymes of the glutathione system. And this is a confirmation that determining the level of markers of oxidative stress and antioxidant activity provides op-

portunities for revealing the active links of the specified pathogenetic conditions. At each stage of the progression of oxidative stress, informative integral indicators are noted, which testify to the effectiveness of protection and the level of damage to biological systems and are predictors of subsequent changes.

Thus, the biochemical mechanism of the development of many diseases of various etiology is closely related to disturbances in the antioxidant defense system and the occurrence of oxidative stress. Under normal conditions, the bodies of clinically healthy people have a balance between pro-oxidative factors and anti-oxidative components consisting of enzymes, vitamins, trace elements and amino acids. Numerous pathological conditions, stress, pollution and other harmful factors lead to a change in this balance in favor of oxidants. The consequence of this imbalance is oxidative stress. The phenomenon of oxidative stress is characterized by the excessive formation of active forms of oxygen (for example, free radicals), which the body is unable to compensate for long-term and which become a trigger for the development of chronic diseases. This especially applies to such diseases as oncological diseases, atherosclerosis and diseases of the gastrointestinal tract. Moreover, the onset and development of neurodegenerative diseases of the central nervous system, such as Alzheimer's disease and Parkinson's disease, are also associated with the destructive effects of free radicals. Further research and a detailed understanding of the specific molecular mechanisms that occur under the conditions of the development of oxidative stress will allow a better understanding of its role in these diseases and will provide an opportunity for more successful application of modern therapeutic approaches and methods.

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