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ROLE OF ACTIVE FORMS OF OXYGEN IN THE AGING PROCESS (literature review)

Abstract. *At oxidative stress the resistance of the organism is achieved by the work of many functional systems. During prolonged stress load the intersystem relations are violated due to unequal functional capabilities of various systems. This leads to disorders in the regulation of the components of functional systems and, consequently, to the emergence of pathological processes. Antioxidant defense system counteracts damaging effects of reactive oxygen to tissues. Inferiority of mobilization mechanisms of antioxidant potential provokes ability of cells to over-production of AFO, which, in general, promotes mutations, tumor growth, their invasion, damage of healthy cells and imbalance between cell proliferation and apoptosis.*
Key words: *oxygen, oxidative stress, aging process.*

It is well known that oxidation processes involving activated oxygen metabolites are essential for the existence of living organisms. They act as inter- and intracellular messengers, modulators and inductors in the regulation of biochemical and metabolic processes. They are the first and the most mobile element in the adaptive restructuring of the body under extreme conditions.

It is marked that the pathological effects occur at the excessive accumulation of AFO, peroxides and their secondary products, more specifically, at the imbalance of pro-oxidant-antioxidant system. This condition is commonly called oxidative stress. There are various factors that cause oxidative stress, and all of them as a result cause oxidative modification of macromolecules. The main of them are the excess of O_2, a significant expression of inflammation with activation of neutrophils and macrophages, ionizing and ultraviolet radiation, smoking, xenobiotics, etc.

It is known that each stressful reaction is normally accompanied by a short increase in the amount of AFO. It is caused by the body adaptation to extreme conditions under which the AFO act as secondary messengers participating in signal transduction and activation of transcription factors and related genes, including those encoding antioxidant enzymes. In normal conditions AFO concentration in tissues is low H_2O_2 - 10^{-8} Mol, $O_2^{\cdot-}$ - 10^{-11} Mol, OH^- < 10^{-11} Mol.

Intensification of the processes of free radical oxidation under AFO leads to increased lipid peroxidation (LPO), oxidative modification of proteins (OMP), destruction of nucleic acids and carbohydrates, which causes structural and metabolic disorders in cells. In most cases OH-, which is able to take hydrogen atom from organic compounds with the formation of free organic radicals, is the initiator of this process:

$$RH + OH \rightarrow R\cdot + H_2O.$$

Lipid peroxidation is supposed to be one of the main causes of damage and death of the cell as a result of AFO action. Also in this way fatty acids are oxidized that can cause violations of integrity and properties of biological membranes. The most significant biomarkers of oxidation of polyunsaturated fatty acids (UFA) are short-alkanes and alkenes, and alkanals, 2,4-alkadienals, alkatrienals, hydroxyalkenal, 4-hydroxyalkenals and their peroxides, malonic dialdehyde, normal aliphatic ketones and izoprostanes.

Lipid peroxidation is a chain reaction that is initiated by the hydroxyl radical, singlet oxygen and is catalyzed by ions of transition metals. The basic reactions of LPO are the following:

$$UFA–H + R\bullet \rightarrow UFA\bullet + RH \quad (1)$$
$$UFA\bullet + O_2 \rightarrow UFA–OO\bullet \quad (2)$$
$$UFA–OO\bullet + UFA–H \rightarrow UFA–OOH + UFA\bullet \quad (3)$$
$$Fe^{2+} + UFA–OOH \rightarrow Fe^{3+} + UFA–O\bullet + OH^- \quad (4)$$
$$Fe^{3+} + UFA–OOH \rightarrow Fe^{2+} + UFA–OO\bullet + H^+ \quad (5).$$

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Thus, LPO starts with knocking out of the hydrogen atom from methylene group of unsaturated fatty acid with radicals (hydroxyl radical, radical of fatty acid or another one) (reaction 1). Produced fatty acid radical reacts with a molecule of oxygen, producing a peroxide radical (reaction 2). Peroxide radicals can take hydrogen atom from another molecules of fatty acid and to reduce to hydroperoxide (reaction 3). Produced radical reacts and there is a chain reaction that can proceed without initiating agents. The ions of iron and other transition metals are involved in spreading of chain reaction (reactions 4,5). Produced lipid peroxides are better soluble in a liquid than polyunsaturated fatty acids, thus they can be easily washed out of the membrane, which promotes self-renewal of membrane structures. Peroxides of fatty acids are unstable, and as a result of disconnection they decompose with the production of highly toxic aldehydes that damage biomolecules of the cell. In contrast to free radicals, aldehydes are stable compounds that can diffuse over large distances. The property of endogenous radicals to cause covalent modification of macromolecules and, consequently, to change the structure of biological membranes, to inhibit the activity of glycolysis and oxidative phosphorylation, the synthesis of proteins and nucleic acids is the base of their damaging effect on the cell.

LPO of endoplasmic and sarcoplasmic reticulum can cause uncontrolled outlet of Ca2 + in the cytoplasm, resulting in violated intracellular conducting of signals, changing of work of enzyme systems, etc. However, LPO is not only destructive process. LPO is significant for renewal of biological membranes, rotation of their protein and lipid components, regulation of physical and chemical properties of the membranes of cells and subcellular structures. Lipids peroxides and low molecular weight products of degradation of oxidized lipids may be involved in signal transduction, which determines the possibility of cell survival or death in stress situations.

Protein molecules are also targets for attack of AFO, which leads to changes in their secondary and tertiary structure, aggregation and fragmentation. Due to the features of the chemical structure and the structural organization of proteins the POM is complex, which is caused by producing of a great amount of oxidized products of radical and non-radical nature. The first stage of POM is eliminating of hydrogen atom from the ά-carbon atom of the polypeptide chain with the producing of carbonyl radical, which rapidly reacts with O_2 with the formation of alkylperoxyradical intermediate compound. This compound can transform into alkoxyradical, which transforms into hydroxyderivative of protein. It is believed that free radical damage of proteins has the same chain nature as the lipid oxidation. The following mechanism of protein (Pr) hydroperoxides at the action of AFO is proposed:

$$Pr + HO\cdot \rightarrow Pr\cdot + H_2O;$$
$$Pr\cdot + O_2 \rightarrow PrOO\cdot;$$
$$PrOO\cdot + e- \rightarrow PrOO-;$$
$$PrOO- + H\cdot \rightarrow PrOOH;$$
$$PrOO + PrH \rightarrow PrOOH + Pr\cdot.$$

The biological role of protein radicals is still not clear, but their ability to acidify other biomolecules confirms their significant role in oxidative damage of biological systems and their oxidative effect. On the other hand, the ability of proteins to react with radical compounds is considered as a manifestation of their antioxidant properties. It was found out, that protein radicals are significant intermediaries at oxidative damage of low-density lipoproteins. It is shown that produced protein radicals can be neutralized with low molecular weight components of the antioxidant defense system, including urates and carotenoids.

The most important aspect of AFO action, due to the biological effect, is their interaction with DNA. About 100 variants of DNA damage by free radicals and modifications of pentose and the nitrogenous bases are identified. It is shown that mitochondrial DNA is damaged in 104 times more frequently than nuclear one. Obviously, this is caused by the fact that most of the AFO in the cell is formed in mitochondria.

Thus, high concentrations of AFO and lipid hydroperoxides inhibit DNA synthesis and cell division and can activate apoptosis

(programmed cell death), which is useful for the organism, because the death of several cells can prevent progression of malignant processes and death of the whole organism. POM, caused by AFO, not just changes the amino acid residues of protein, but also violates its tertiary structure and even causes its aggregation and denaturation. As a result various functional activities of protein (enzymatic, regulatory, participation in matrix synthesis, transport of ions and lipids) decrease or disappear, and some of them promote mutations or become autoantigens.

Increasing of concentrations of AFO, due to the displacement of equilibrium between the processes of their producing and detoxification, is a precondition for violation of functional activity of cells and the development of pathological processes and aging.

Protection is carried out in two fundamentally different ways:

1) a decrease in the producing of the first AFO - by reducing of O_2 content in the cell or its faster use by respiratory chain;

2) functioning of antioxidant system (AOS).

Hence, the failure of antioxidant protection due to any external influence (negative factors of the environment) intensifies the free radical oxidation. This is accompanied by changes in the conformation of lipids, which leads to disruption of structural and functional properties of biomembranes, increasing their lability and permeability, imbalance of enzyme membrane systems, disorder of electric transport chains of mitochondria, which leads to more systemic violations of the tissues and organs of the body.

Conclusions. 1. Reactions involving reactive oxygen are the most significant processes in mechanisms of self-regulation in the body.

2. The free radical oxidation (FRO) at the action of AFO is manifested in cellular metabolism both at normal state and at pathology. Intensifying of FRO processes may be the evidence of intoxication, leading to oxidative stress, which is a key part of most pathological processes.

3. With age there is hyperactivation of free radical processes in organs and tissues, that leads to irreversible damage of the membrane structures, change of their permeability and cell death, that affects the functioning of tissues, organs and whole organism.

4. The factors that stimulate the formation of reactive oxygen are the interaction of cells with foreign materials (with viruses, infection, abnormal proteins, xenobiotics), their interaction with free radicals of fatty acids, radioactive radiation, membrane active compounds and stress.

5. At oxidative stress the resistance of the organism is achieved by the work of many functional systems. During prolonged stress load the intersystem relations are violated due to unequal functional capabilities of various systems. This leads to disorders in the regulation of the components of functional systems and, consequently, to the emergence of pathological processes

6. Antioxidant defense system counteracts damaging effects of reactive oxygen to tissues. Inferiority of mobilization mechanisms of antioxidant potential provokes ability of cells to over-production of AFO, which, in general, promotes mutations, tumor growth, their invasion, damage of healthy cells and imbalance between cell proliferation and apoptosis.

7. The state of antioxidant system depends on the course and metabolic activity of activity of endogenous antioxidants. Consistent and continuous functioning of these mechanisms enhances protective functions of the body, prolongs life and prevents aging of the organism.

8. It is established that aging is accompanied, on the one hand, by changes in production of FRO or AFO, and on the other hand - by significant changes in the AOP system, including decreased activity of its enzyme chain.

9. The use of antioxidant drugs can promote the normalization of extreme changes in the producing and utilization of active forms of oxygen, modulating the activity of antioxidant enzymes in order to maintain the adaptive capacity and detoxification properties of the organism.

10. Since FRO involving active oxygen radicals is one of the leading universal mechanisms of cell damage, the evaluation of the state of this process is recommended to be included as one

of the methods for monitoring of health, including during treatment and preventive measures.

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