# MEMBRANE-STABILIZING EFFECT OF ANTIOXIDANTS

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***Abstract.*** *In addition to the four - electron reduction of O2, processes leading to the formation of superoxide anions and hydrogen peroxides are also possible in biological systems. When exposed to super oxides and peroxides, more toxic hydroxyl radicals are formed.*

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In addition to the four - electron reduction of O2, processes leading to the formation of superoxide anions and hydrogen peroxides are also possible in biological systems. When exposed to super oxides and peroxides, more toxic hydroxyl radicals are formed. They are one of the most probable activators of lipid peroxidation of polyunsaturated fatty acids of phospholipids (LPO) with the formation of alkyl radicals (R), which promotes the free radical oxidation of lipids. It occurs under the influence of various agents, which include CCl4 and heliotrin. These agents penetrate the cells well, where they metabolize while forming trichloromethyl, chlorines and pyrroles, which enhance LPO.

The accumulation of LPO products in the body of rats with toxic liver damage by xenobiotics (heliotrin, CCI4) leads to an increase in the permeability of lysosome membranes up to their rupture with the release of hydrolases into the inner space of the cell and lysis of cellular contents. Massive release of lysosamal enzymes (phospholipases, sialidases , DNases, b-galactosidases, b-glycosidases, etc.), leads to degradation of their substrates:phospholipids, gangliosides, DNAs, etc. In parallel, there is an accumulation of Ca ions in the cystosol of cells, this process also led to degradation of cell membranes. Therefore, it occurs to be a topical issue in the pathogenesis of diseases to identify the intensity of LPO processes in organs, to identify damage caused by this process at the molecular and cellular levels, paying attention to the qualitative and quantitative composition of the components of cell membranes: phospholipids, gangliosides, proteins, etc.

This fact proves a violation of the stabilization of membranes, a violation of the activity of the antioxidant system of the body. Tocopherols function in membranes as a kind of molecular "channel" through which free radical centers leave the hydrocarbon zone of membranes. Tocopherol molecules have a long hydrocarbon chain containing periodically arranged methyl substituents (4, 5, and 6). The lateral methyl groups of these chains are packed into so called "pockets" formed by unsaturated bonds of fatty acid residues, forming close complexes stabilized by van der Waals forces. This leads to a denser packing of hydrocarbon chains, which results a restriction of the penetration of reactive oxygen species deep into the hydrophobic layer of the membrane. (2, 3, 17, 18, 19.)

Tocopherols influence the qualitative composition of membrane phospholipids, provide a prerequisite for the assumption of the ability of tocopherols to be directly included in their composition, normalize the activity of phospholipase A2, increase the total phosphorus content of phospholipids, mainly due to an increase in the content of phosphotidylcholine (PC) and phosphotidylethanolamine (PE) fractions (20,21,23.) The activity of mitochondrial respiratory

chain enzymes, ubiquinone, succinate dehydrogenase, cytochrome oxidase increases, under the influence of vitamin E.

The membrane stabilizing effect of tocopherols is reduced to the main molecular mechanisms:

1) Interaction with phospholipid peroxide radicals

2) Quenching of singlet molecular oxygen

Regulation of the molecular mobility of the lipid layer of biomembranes

Protection of membranes from the action of phospholipases (5,6,7,8,10)

Tocopherol stabilizes the phospholipid bilayer in two ways:

1) Stabilization of the lipid bilayer by van der Waals interaction of methyl groups of a-tocopherols with unsaturated double bonds of phospholipid fatty acids

2) Stabilization of polypeptide chains of integral proteins. The biological effect of tocopherols reveals the following important facts:

a) Tocopherol protects unsaturated lipids from peroxidation.

b) Tocopherol is involved in the processes of biosynthesis of heme-containing proteins (with E-vitamin deficiency, heme synthesis is disrupted).

c) Tocopherol participates in intracellular processes of oxidation and oxidative phosphorylation; d) tocopherol is necessary as a dietary factor contributing to the assimilation of polyunsaturated fatty acids in the intestine.

e) Tocopherol protects against oxidation of selenium compounds. Tocopherols exhibit hepatoprotective effects prevent the damaging effect of hepatotoxins (CCI4 and ethanol). Vitamin E collaboratively with selenium increases the activity of glutathione peroxidase.(15,22) The use of vitamin E at a dose of 20 and 30 mg / 100g and sodium selenite subcutaneously at a dose of 100 mcg / kg for the treatment of animals with toxic tetrachloride hepatitis gave the survival rate of animals 100% with 20% death of poisoned animals. They increase the activity of glutathione peroxidase, glutathione reductase, superoxide dismutase, succinate dehydrogenase, RNA transferase and RNA ligase. Therapeutic and biochemical studies show that sodium selenite and vitamin E enhance the effect of each other.(11,12,13) There are 3 main processes with their participation:

1) Prevention of fatty acids from oxidation

2) Destruction of peroxides

3) Suppression of the formation of free radicals

However, in order to optimize the effect of antioxidants such as sodium selenite and vitamin E, it is advisable to use carrier systems such as liposomes. To date, liposomes seem to be the most promising compared to other carriers, not only because they are biodegradable and easy to manufacture, but also because of their affinity with natural cell membranes in chemical composition, because of the huge variety of their sizes and other structural parameters, which determine the variety of possible mechanisms of liposome interaction with biological objects.(7,8,9.14)

A number of authors revealed that liposomes meet the following criteria:

1) Absence of cytotoxicity;

2) Immunological inertia (with the exception of special antigen transport); 3) the efficiency with which molecules are incorporated into the carrier, under conditions in which the properties of the included substance are not violated or inactivated;

4) the ability to protect the transferred substance from damage or destruction

5) the efficiency with which the transferred substance in combination with the carrier is being delivered to cells.

Liposomes are small spheres containing water compartments separated from each other and from the external aquatic environment by closed bilayers of phospholipids, which are oriented in the bilayer as well as in biomembranes . Hydrophilic (polar) heads are facing outward, into the aqueous phase, and hydrophobic (nonpolar) segments are facing inside the bilayer and tend to avoid contact with water. Depending on the size, there are small single-layer (diameter 25100 nm), multilayer large (diameter 0.2-2 microns) liposomes.

Initially, liposomes were used as models of biological membranes to study the functions of membranes, and then they began to be used as "containers" for the delivery of various drugs to organs and tissues. (13, 14, 16)

Drugs encapsulated in liposomes have a great therapeutic effect: the duration of the drug increases, and its dose can be significantly reduced.

Many authors assume that there are two ways of their penetration into the cell: 1) the liposome is captured by the cell due to endocytosis; 2) the liposome merges with lysosomes, whose phospholipases hydrolyze the phospholipids of the liposome membranes, which ensures the release of the drug into the cytoplasm of the cell, and the lipid component is embedded in the membrane (13, 14). In both cases, the substance encapsulated in the liposome enters the cell despite the membrane barrier. An hour after the injection of liposomes to rats, the liver will contain from 24 to 75%, spleen from 6 to 18%, lungs from 1.5 to 16% of liposome phospholipids. The effectiveness of using liposomes as drug carriers largely depends on whether they will be able to maintain their integrity and deliver the drug to the right organ, since there are obstacles that liposomes need to go through. One of them is the macrophages of the reticuloendothelial network, which need to be blocked by injectioning empty liposomes first, and then liposomes loaded with drugs.

The next obstacle is blood serum. Liposomes can be exposed to lipoproteins that try to exchange their lipids with liposomes and thereby contribute to their destruction and leakage of contents. To increase the resistance of liposomes to the action of lipoproteins, cholesterol is injected into the liposomes. The successful use of liposomes as drug carriers depends on the affinity of liposomes to target organ cells, which is increased by adding gangliosides to the composition of liposomes. Especially increased transport of liposomes in the liver is observed after the inclusion of CMI ganglioside in their composition.

Exogenous gangliosides selectively bind to liver parenchymal cells , embed in membranes, and then pontaneously incorporate into the phospholipid bilayer . It is assumed that when liposomes interact with cells, an intermembrane exchange of lipids occurs. Phospholipids of liposomes restore the functions of cell membranes and enhance their ability to resist the penetration of active oxygen radicals. Thus, it can be proposed that liposomes have a membrane-stabilizing and antioxidant effect.

Attempts are being made to use liposomes and phospholipid preparations for the repair of hepatocyte membranes affected by liver diseases. Hereby, the following phospholipid preparations were administered to rats with toxic heliotrine hepatitis : phosphatidylcholine (FCHL) (from cotton), soy phosphatidylcholine (“Naterman”company), as well as a drug which includes phosphatidylcholine and potassium salt of glycyrrhizic acid (PC+ GA). The greatest effect among

these drugs was the drug PC + GA. With intraperitoneal administration of it to rats, the activity of aldolase was normalized. Intraperitoneal administration of egg PC reduced hyperfermentemia, while intravenous administration had no effect. Apparently, phospholipid drugs injected into the bloodstream can be attacked by blood cell elements or undergo lipase cleavage in the bloodstream, which reduces their effect on hepatocytes, therefore intraperitoneal administration of drugs is more efficacious.

Liposomes formed from total phospholipids are better absorbed by hepatocytes than phosphatidylcholine ones. The solubility in water or in a hydrocarbon solvent of some drugs enclosed in a liposome affects the degree of assimilation of liposomes by cells. The greater the solubility of the drug in water, the more it will be included in the internal water space, and the greater its solubility in a non-polar solvent, the more it can be enclosed in hydrophobic regions of liposomes. In the process of interaction of liposomes with cells, the surface charge and the physical state of phospholipids happens to be important. It is believed that "liquid" liposomes effectively merge with membranes.

Apparently, liposomes formed from total phospholipids isolated from healthy rat tissues meet the above requirements, and the inclusion of antioxidants in them - vitamin E and sodium selenite will have an even greater effect in preventing membrane degradation in liver pathology in rats diseased by hepatotropic poisons.

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