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SEARCH FOR ANTIOXIDANT THERAPY MEANS BY KINETIC METHODS

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At the present time the hypothesis about biomembranes' permeability disturbance due to the lipid peroxidation intensity change has been adopted as the molecular mechanism of many pathologies' development. A special attention is paid to the mechanism of free radical aging, adaptation to the silent epidemic, labour activity regime and also cancerous diseases development [2].

For prevention and treatment of various physiological states and pathologies an antioxidant therapy is widely used [1, 4]. It is evident that in the progress of the therapy is possible on the basis of effective antioxidant testing methods development. All the known antioxidants are divided on their physicochemical properties into hydrocarbon soluble ones and their water soluble derivatives. Kinetic approaches are developed for water insoluble antioxidants testing. For this purpose the chain interruption velocity constants in the inhibitor (K_t) or the induction time of ethyl benzene, cumene, styrene, decalin oxidation in the presence of phenols and aromatic amines [3, 5] are used. For lipid oxidation processes inhibition we offered a methyl linoleate model. For this purpose the methyl linoleate oxidation kinetics in the solution of benzene chloride at $60^o \pm 0{,}2\ ^oC$ at the presence of the initiator depending on the concentration of 2,6-ditretbutil-4-methyl phenol (ionol), 2, 5, 7, 8-tetra methyl-2-(4, 8, 12-trimethyl tridecyl)-6-oxichromane (α-tocopherol). The participation of ionol is shown in the chain interruption reaction only. The chain interruption velocity constant in ionol equal to $(2{,}6\pm0{,}4)\cdot10^4\ l\cdot mol^{-1}\cdot c^{-1}$ is defined by kinetic research methods. Similar calculations of K_t for α-tocopherol showed their changes depending on concentration and complicated mechanism of its action. For such inhibitors' efficiency estimation the method of mathematical treatment of kinetic curves (KC) by means of their approximation by functions and the following differentiation. As a result of this approach five kinetic parameters, which allow the inhibition efficiency to be evaluated on the initial velocity and inhibition time. On the maximum velocity, acceleration and acceleration time finish the mechanism of the inhibitor's action is evaluated.

However, the biomembranes' lipids conditioning the level of free-radical oxidation, the biomembranes' permeability change and the development of pathologies represent water-emulsion systems including amino acids, proteins and enzymes. That is why bio-adequate models are needed to search the means of antioxidant therapy. To select such a model the micelle formation of ethyl oleate has been investigated. For this purpose the micelle formation in two- and three-component systems has been studied first of all: ethyl oleate – water; ethyl oleate – water – emulsifier. On the minimal value of the critical concentration of micelle formation the composition of water-lipid substrate including ethyl oleate and water in the ratio 1:3 (in volume) and cetyl trimethyl ammonium bromide as emulsifier in the concentration of $(1–3)\cdot10^{-3}$ mol/l was defined.

Further, the kinetics of the water-lipid substrate oxidation at the presence f salts $CuCl_2$, $FeCl_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$ depending on the concentration was studied. It was shown that the most active catalyst is cupric chloride, and the activity of other salts falls off in the series $Cu^{2+} > Fe^{2+} > Fe^{3+} > Co^{2+} > Ni^{2+}$. In further investigations cuprum cations in the concentration of $(1–3)\cdot10^{-3}$ mol/l were chosen as a catalyst.

For the estimation of antioxidant testing possibility in the water-lipid substrate the influence of ionol

depending on the concentration was studied first of all. It was shown that the chain interruption velocity constant (K_t) decreases regularly with the increase of ionol concentration, that testifies to its complicated mechanism of action. For the estimation of antioxidant properties of the compounds tested two approaches have been offered: the external standard and KC mathematical treatment methods, as it is described above. By the external standard method the character of substrates oxidation KC at the presence of ionol and the inhibitors tested is compared in similar conditions. With the help of the water-lipid model the testing of antioxidant properties of the following preparations was carried out: α-tocopherol, capoten, paracetamol, osalmide and emoxypine. It was shown that α-tocopherol in the water-lipid system demonstrates its buffer action: at concentrations from $1 \cdot 10^{-3}$ to $1 \cdot 10^{-1}$ mol/l it accelerates the process, at lower concentrations renders a weak inhibitory effect. Capoten manifests itself as a strong inhibitor - arrests the oxidation process, that corresponds to full inhibition period presence, then the acceleration of the process and production of control velocity take place. The full inhibition period is in proportion to the concentration of capoten. Osalmide also manifests itself as a strong inhibitor. Paracetamol and emoxipyne act as weak inhibitors; they only inhibit the initial oxidation velocities without providing periods of full inhibition. But in the presence of paracetamol and emoxipyne a decrease of the maximal velocity proportional to the concentration is registered, that testifies to the possibility of their oxidation products' participation in the chain interruption.

As far as microelements are represented in the cell in the form of coordination compounds (CC) with amino acids, for the development of antioxidant therapy means testing methods the inclusion of amino acids into the water-lipid system is of great interest [6].

For this purpose the water-lipid substrate kinetics at optimal pH in the presence of cuprum CC with every of the amino acids: α-alanine, valine, threonine, lysine, phenyl alanine, leucine, serine, histidine – has been studied. Thereat the concentration of cuprum cations made $2 \cdot 10^{-3}$ mol/l, and that of an amino acid - $1 \cdot 10^{-2}$ mol/l. An amino acid abundance, which guarantees the complex stability in the substrate, was foreseen. As a result the lack of activity in threonin and lysine, weak inhibitory activity in histidine and serine, a stronger inhibitory activity in leucine and phenyl alanine were found out.

On the basis of these results a bio-adequate method of antioxidant therapy means testing with cuprum coordination compound and α-alanine participation is being developed.

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