Introduction

The enhancement of general and special physical workabilities of athletes under the influence of high physical loads under conditions of rapid processes of restoration and prevention of the state of overtraining are important components of the realization of an athlete as a professional and the support of his/her health and life quality (Гуніна, 2011). One of very solid components of the appearance of overfatigue and a decrease of physical workability is the activation of lipid peroxidation (LP) at a simultaneous decrease in the activity of endogenous antioxidative system, which constantly accompanies physical loads and induces the development of such pathobiochemical phenomenon as oxidative stress (OS) (Deminice et al., 2011).

Under conditions of ordinary stress situations and insignificant relative hypoxia, which accompanies moderate-intensity physical loads, the activation of LP in organism is bounded. This is ensured by the continuous functioning of powerful antioxidative system, which counteracts the lipoperoxidation in all links. However, the super intense physical loads in a combination with the emotional stress (e.g., during the competitions), which is characteristic to high-achievement sports, induce a significant...
activation of LP, whose products are evaluated in this case as markers of the intensity of previous physical load. The fracture of cell membranes by free radicals, accumulated in the process of LP, is one of the essential factors of a fatigue characterized by violations of the resynthesis of ATP and the course of regenerative processes. In addition, it was shown in the recent years that the long-term intense physical loads can induce the process of apoptosis of cells of human blood (Wang, Huang, 2005), which surely will negatively affect the parameters of workability, in particular, the aerobic one. A decrease in the activity of enzymatic systems, including the antioxidative and detoxicative ones, on the level of holistic organism, which happens under physical loads, extends the period of restoration after training exercises and complicates the formation of a required level of adaptive mechanisms (Hüttemann, 2013).

**General characteristic of some natural antioxidants and their participation in the regulation of physical workability stimulation processes**

Even those above-presented scanty facts indicate the metabolic foundation for the necessity to apply antioxidative agents under physical loads. Since the schemes of pharmacological support of sport training include very frequently simultaneously 5-7 and more pharmacological agents, the attempts to determine a mechanism of action of such antioxidative agents that would have a complex directedness of their action, seem to be expedient. We note that their application during athletes’ training has no, with the rare exception, purpose to determine the biochemical mechanisms of ergogenic properties appearance. Therefore, the application of antioxidants with the aim to stimulate the physical workability requires the establishment of their action mechanism, which should be based on system-forming factors. From our viewpoint, one of the most important items is the ratio of prooxidative and antioxidative factors. On the basis of the analysis of modern literature data, it was shown that the action of LP processes is the universal property of ergogenic pharmacological substances and is of high importance (Гуніна, Носач, 2012). The results of executed studies of the action of pharmacological antioxidative agents in model systems proved that the estimation of the ergogenic mechanism of their effect is also significantly based on the membranotropic character of their influence on organism (Ляхов и др., 2007), which is closely related to the presence of antioxidative properties (Гуніна, 2010). With regard to the fact that the metabolitotropicity as a phenomenon is more inherent to natural substances, the determination of fine mechanisms of influence of pharmacological agents of the antioxidative directivity, in particular, natural ones, on the physical workability is the goal of the present review.

In our opinion, the primary mechanism of influence on athletes’ organisms is the antioxidative action, which is established in numerous studies and is revealed, in the first turn, on the membrane level. The prevention of a structural-functional reconstruction of cellular membranes is a factor that favours the running of energy-generating processes, promotes an increase of the immune defence, and improves the course of the processes responsible for a decrease of the content of lactate accumulated during physical exercises in training process and in competitions. This last factor is of high importance for a deceleration of the subsequent processes related to changes of pH in organism, in particular, to changes of the activity of kallicrein-kinin system and the system of aggregate state of blood regulation, which positively affects the adaptive reconstructions of organism during physical loads (Donde et al., 2012). In addition, the implementation of the antioxidative mechanisms of ergogenic influence of antioxidants depends strongly on the regulatory effect on the level of erythrocytes membranes, since it favours the improvement of the shape and size of blood red cells, which is accompanied by a corresponding improvement of oxygen transfer processes.

The ergogenic effect of such natural antioxidants as, for example, ceruloplasmin and polyunsaturated ω-3 fat acids is realized mainly through the regulation of membranes structural-functional state. As is known, the improvement of a blood turnover in micro vessels and an increase in the saturation of tissues with oxygen are attained due to the correction of functional state of membranes of blood red cells (Гуніна, 2013). This is a crucial factor improving the oxygen-transporting function of blood. By substantiating the study of natural antioxidants as ergogenic agents, we started from the mechanism of regulation of a blood turnover in skeletal muscles and their saturation with oxygen through positive changes in the structure and the functional state of erythrocytes. The owned data on the modelling influence on membrane damage
due to the action of oxidative stress under physical loads, which were obtained in a quantum-chemical model, and experimental studies (Gunina et al., 2013) were confirmed by the results of subsequent studies in vivo by the author (Гуніна et al., 2007; Oliynyk, Gunina, 2008). It was established that the improvement of cellular structural-functional state, in particular, erythrocyte membranes is accompanied by an increase of the indicators of general and special work abilities of athletes, which coincides with the presence of interrelations between the pharmacological efficiency of antioxidative preparations and their ability to stimulate the physical workability and durability of athletes (Teleglów et al., 2011).

One of the most powerful natural antioxidants is ceruloplasmin, which is copper-containing oxidase (EC 1.16. 3.1) of the α-globin fraction of blood plasma of animals. The antioxidative action of ceruloplasmin is well known but the information about its properties related to the normalization of a structural-functional state of membranes, including erythrocyte ones, in athletes are scanty. In the problem of metabolic aspects of adaptive reconstructions under physical loads, the attention is traditionally paid to reconstructions of the structure of skeletal muscles and to the acceleration of the processes of energy formation in mitochondria (Hawley, 2002). As for the consideration of the role of ceruloplasmin under physical loads, only its antianemia properties connected with the iron transfer are discussed (Kenyon et al., 2011). There are few studies available where the very significant role of structural-functional reconstructions of erythrocyte membranes related to the development of hypoxia in tissues is emphasized. In particular, it was shown that patients suffering from chronic cardiac insufficiency reveal a high micro viscosity of plasmatic membranes of erythrocytes, in which the polar groups of lipids are closely arranged, is registered. This causes a subnormal content of oxyhaemoglobin - an increase of the number of complexes of haemoglobin with nitrogen oxide, and a change in the bonds of nitrogen oxide with haemoglobin (Шереметьев et al., 2013). Therefore, from our viewpoint, involving, respectively, the recognition of an important role of the oxygen-transporting function of blood in the physical workability growth process, especially of the aerobic character, the application of antioxidants with accompanying membrane-protecting properties, to which ceruloplasmin is referred, is very expedient in the process of athletes’ training. It is worth to note that this postulate so far concerns so far only the antioxidants of nonenzymatic character.

The analogous mechanism of influence on the physical workability is inherent to the domestic antioxidative preparation Epadol on the basis of ω-3 polyunsaturated fat acids (PUFAs), in the first turn, eicosapentaenoic and docosahexaenoic ones. The preparations of ω-3 PUFAs, which are essential for men/women, recently attract more and more attention. The pharmacological studies of PUFAs are intensively carried out all over the world. However, the molecular mechanisms of development of their therapeutic effects are not established finally and such studies are practically absent in sport area. At the end of the XXth century, Ukrainian scientists put the preparation Tekom on the pharmacological market. It is a mixture with a high (at least 43.0 %) content of ethers of animal ω-3 polyunsaturated fat acids as well as palmitoleic, palmitic, linolenic, linoleic, and oleic ones. Its modern analogy is the Ukrainian preparation Epadol. For it, the quantum-pharmacological forecasting with the help of the software PASS Inet and with the use of the QSAR (Quantitative Structure-Activity Relationships) principles, i.e., with regard for the quantitative interconnection of the structure of molecules and their activity, was performed. The results allows one to assume with a high probability that the number and mutual arrangement of unsaturated bonds in molecules of PUFAs (eicosapentaenoic and docosahexaenoic acids) that enter, as the basic ones, to the composition of the preparation Epadol determine the antioxidative and, respectively, mediate ergogenic properties of given compounds, which are very useful at the application to athletes’ training practice (Гуніна et al., 2007). The introduction of medicinal agents on the basis of PUFAs to the programs of pharmacological support decreases as it is testified by the data of recent studies on the risk of coronary diseases and sudden coronary death, especially in young athletes (Ramel et al., 2010). The results of this work by A. Ramel et al. (2010) proved that the introduction of fish oil to the ration of athletes favours the improvement of a state of erythrocyte membranes at the expense of an increase of the contents of unsaturated fat acids in them. This improves a structural-functional state of membranes and favours the mechanisms of energy supply for the muscular activity.
Presently one of the modern directions of organism homeostasis support is the use of probiotic substances on the basis of various microorganisms’ strains. However, this aspect is slightly studied in the area of sport pharmacology, since the basic mechanisms of influence of medicinal agents on those metabolic links that are responsible for its ergogenic action under physical loads are not clarified. It is only known that probiotics not only hamper the appearance of dysbacteriosis but they are also able to produce biologically active substances such as vitamins, aminoacids, antitoxins, etc. and to control the level of pH of the medium where they are placed. It is considered that one of the most efficient probiotic agents for the support of organism microbiocenosis are those with the basis of the strain Enterococcus faecium L-3 (Kolodjieva et al., 2006). The probiotic functional product Sporting Laminolact developed by the Russian scientists on the basis of the strain E. faecium L-3 contains, in addition to live bacteria, carrot, dog rose, and vitagmal (extract of cells of the subtropical medicinal plant of the family of Aralia Poliascias Filicifolia), which ensure the powerful antioxidative action. It was shown that the action of this probiotic on athletes’ organisms improved the functional state of erythrocyte membranes and decreased the content of toxic substances in blood serum, i.e., decreased the manifestation of the syndrome of endogenic intoxication characteristic of intense physical loads (Гунина, 2012). The decrease of manifestations of the endogenic intoxication of organism causes, in turn, the improvement of the function of myocardium, enhancement of the tolerance to loads, stimulation of immunity, and enhancement of the resistance to viral and bacterial infections, which is one of athletes’ metabolic foundations of the ergogenic action of pharmacological probiotic agents.

According to our data, the depressive changes of segment ST (13.4 %) and complex QRS (9.9 %) as well as the frequency of the appearance of early ventricles repolarization syndrome (7.9 %), are essentially rarely observed on electrocardiograms of athletes at the application of Sporting Laminolact. In complex, this indicates the improvement of the contractive ability of myocardium and, hence, the functional state of one of the main organism systems, which limits the physical athletes’ workability, namely the heart-vessel system (Гунина, 2011).

Biochemical mechanisms of implementation of antioxidative agents influence on the formation of physical workability

At our glance, the primary link of an implementation of the ergogenic action of such agents is the deceleration of the activity of POL processes with simultaneous increase in the degree of antioxidative protection, in the first turn, on the level of cellular membranes. This causes, in turn, the improvement of structural-functional properties of cytoplasmatic membranes. For example, for erythrocytes as an adequate model of the total pool of cellular membranes of organism, this means the normalization of the shape and volume of cells with a subsequent decrease of their aggregative properties (Antonova et al., 2011). It is established that the improvement of a structural-functional state of membranes of blood red cells is accompanied by an increase in the content of ATP in them (González-Alonso, 2012), which is one of the most significant factors of the productive functional activity of erythrocytes. These two factors are direct components of microcirculation processes improvement, which ensure mainly the supply of oxygen to skeletal muscles. We may consider that, since ATP is a powerful vasodilatatory agent, this molecule can be a key mediate regulator of the micro vessel reaction in various tissues at a change in their saturation with oxygen. In other words, the researchers connect the transfer of oxygen in vessels of the microcirculatory channel with changes in the content of ATP in erythrocytes. On the other hand, increase in the content of ATP in cells as a factor of the improvement of their functional state and the operation productivity, in particular, the ionic permeability and the contractive ability, is characteristic, under physical loads, of the cells of skeletal muscles and cardiomyocytes, which is confirmed by the data of modern studies executed with the use of novel technologies (Zhu et al., 2014). In other words, the improvement of a structural-functional state of cellular membranes and those of the cells of skeletal muscles and myocardium is the mediate way to the increase of physical workability of athletes due to the acceleration of the transport of oxygen under training and competitive loads.

The recent data testify convincingly that the intense physical loads, in particular, in the high-skilled representatives of cycling sport types with the aerobic mechanism of energy provision cause the appearance of violations, with a high frequency
of manifestations, of the expression of the majority of genetic markers of mitochondrial biogenesis, which is accompanied by subsequent changes in the processes of energy provision. These processes are mediated through a change in the activity of matrix RNAs (mRNA) (Psilander et al., 2010). It is also shown that at intense physical loads, especially inherent to the stage of a direct preparation to competitions, the level of transcription of genes determines the activity of autophagocytosis as it increases by 49-57%. At the same time, the activity of mRNA of one of the lysosomal enzymes - cathepsin L - grows reliably by 23% (Jamart et al., 2012), which indicates the acceleration of the processes of limited proteolysis with the help of lysosomal proteinases, which enter the circulatory system. This testifies to the benefit of the data on an increase of the content which enter the circulatory system. This testifies to the benefit of the data on an increase of the content of products of the uncompleted proteolysis (namely, molecules with medium molecular mass as markers of the endogenic intoxication) under the influence of physical loads (Гуница, 2012). We cannot but mention the fact of a normalization of the permeability of cytoplasmatic membranes, which is disturbed under intense physical loads, due to the influence of antioxidants because this is also a factor preventing the ejection of the excess of lysosomal enzymes accumulated at metabolic reconstructions outward (Mila-Kierzenkowska et al., 2012). The ejection of lysosomal proteinases into the extracellular matrix and, finally, into blood is accompanied by the excessive activation of many humoral regulators, in particular, the kallikrein-kinin system, various pro- and anticoagulative links of the system of regulation of the aggregative state of blood, renin-angiotensin system, etc., which cause the uncontrolled violations of homeostasis and the appearance of a fatigue in athletes with the decrease of physical workability (Ribeiro et al., 2007).

One more important side of the negative influence of disturbances of a structural-functional state of cellular membranes of organism is a deterioration of the contractive ability of myocardium. It is shown that the membranes of myocardiocytes and erythrocytes are very sensitive to the manifestations of OS and accompanying hypoxia of tissues (Ellison et al., 2011). This affects the functional state of myocardium so that the ejection fraction and the impact, and minute volumes of blood decrease, whereas the final-diastolic volume increases. In this case, the expression of a cardiac dysfunction correlates with the expression of manifestations of oxidative stress (the accumulation of methylguanidine in blood and of products of the reaction with thiobarbituric acid (MDA) in myocardium) and the content of the commonly used marker of a dysfunction of myocardium, the MB-fraction of creatinephosphokinase (Hsu, Wang, 2012). It is of high importance that such manifestations of a cardiac dysfunction, as is testified by the data of the above-cited experimental studies and by clinical results (Schwedhelm et al., 2003), can be prevented by the application of ascorbic acid, α-tocopherol, curcumin, polyphenols (in the first turn, resveratrol), quercetin, rutin, etc, i.e., various natural antioxidants. Thus, the numerous data of the modern literature are consistent in the following. Since oxidative stress is one of the most spread and universal mechanisms of appearance of a fatigue in athletes, it is possible to moderately control the ergonic properties of organism by preventing the metabolic consequences of OS by means of the use of pharmacological antioxidative agents.

We cannot but dwell on such aspect of negative consequences of the activation of OC as the ejection of catecholamines with the following coronary spasm. The appearance of oxidative stress breaks the natural balance between the pro- and antioxidative systems of organism, which is a reason for the destructive action of active forms of oxygen that can independently be, quite probably, the inductors of a spasm of coronary arteries. Hence, the peculiar vicious circle is formed: an increase in the concentration of catecholamines causes a sharp increase in the production of active forms of oxygen, which is inherent to the activation of POL processes. In turn, these forms can induce coronary spasm and the exhaustion of antioxidative reserves, which leads to the manifestation of the overstress of cardiac muscles in athletes, by finally resulting in the intensification of free-radical processes in myocardium. Thus, the activation of endogenic mechanisms of generation of active forms of oxygen is accompanied by the load on the system of antioxidative protection and the development of OS, which is the essential link of the pathogenesis of a damage of myocardium under physical loads in experimental studies and observations of athletes and is one of the most crucial factors of physical workability decrease. This fact, which is based on the mechanism of activation of biologically active amines in the course of a disturbance of the pro- and antioxidative balance (PAB) in organism,
substantiates additionally the necessity of the application of antioxidative agents in order to prevent any changes of the contractive ability of cardiac muscles.

It is worth noting that the active forms of oxygen accumulating at oxidative stress of various origins can manifest themselves, as is known, as apoptogenous stimuli (Magenta et al., 2011), whose mediate action causes the breaking of the integrity of various cells of organism (myocytes, cardiomyocytes, macrophages, thymocytes, erythrocytes, etc.). Therefore, it is unquestionable that the antioxidants can be also used for a modification of such process significant for live organisms as the programmed cellular death (Park et al., 2014). It is shown that an increase in the level of reactionable forms of oxygen in the course of training, for example, in red fibbers of skeletal muscles, causes a decrease in the antiapoptotic ability of cells (index Bcl-2/Bax) (Liu, He, 2013). Moreover, irrespective of the genesis of apoptosis (hypertonia, electromagnetic oscillations, malignant neoplasms, Helicobacter pylori-associated diseases), the application of various antioxidants such as melanin and vitamins C, A, and E is accompanied by a decrease in the number of apoptotically changed cells and in the activity of the enzymes caspases, in particular, caspase-8 (Magenta et al., 2011). The use of inhibitors of caspases (benzyloxycarbonyl-l-Val-Ala-Asp fluoromethylketone) or blockers of the reaction-active forms of oxygen accumulating at oxidative stress (manganese superoxide, disodium salt of 4,5-dihydroxy-1,3-benzene disulfonic acid) leads also to the prevention of the appearance of apoptosis (Vandenabeele et al., 2006). Relative to myocardium, the uncontrolled apoptosis means a disturbance of the contractive ability of this tissue and, hence, the corresponding decrease of physical workability. In addition, it is well known that the process of destruction of normal myocardiocytes participates in the development of pathological hypertrophy of myocardium under physical loads (Boyle et al., 2011), which is one of the most important factors of a decrease in the physical workability and a weighty factor of the sudden coronary death of athletes. It is shown that the fragmented mono- and oligonucleosomes, whose contents are determined by the immunoenzymatic method, Bcl-2, Bax, Apaf-1, AIF, split fragments of PARP, split caspases-3, split/active caspases-9, heat shock protein (HSP 70), etc., determined by the Western Blott-analysis, can be markers of apoptosis in skeletal muscles and myocardium under physical loads (in experiment) (Siu et al., 2004). However, according to the viewpoint of those researchers, the intensity of apoptotic changes depends on the intensity of physical loads, i.e., on the expression of oxidative stress. Their coupling is proved by the determination of the degree of activation of the antioxidative enzymes Cu/Zn- and Mn-superoxide dismutases. On the basis of these data, it is possible to assert that the control over the training process (volume, orientation, and intensity of physical loads) at the appropriate antioxidative accompaniment opens a way to the deceleration of the process of programmed cellular death.

In addition, it is necessary to mention the fact that specific long-term physical loads during the process of adaptation and the oxidative stress associated with them can induce the deceleration of genes expression, in particular, of mRNA, interleukin 6 (IL-6), receptor of IL-6, insulin-like growth factor, phosphofructokinase, and the transport of glucose (Leandro et al., 2011; Friedmann-Bette, 2012). Since the final consequence of these genes activation is the improvement of energy provision mechanisms and the resistance of organism to negative external factors, it is quite reasonable to consider that the application of antioxidative agents and the normalization of disturbed PAB in organism under physical loads will positively affect the fine mechanisms of implementation of the manifestations of the arisen oxidative stress.

Thus, oxidative stress accompanying the intense physical loads in athletes causes violations of a structural-functional state of cellular and subcellular membranes, which is a factor provoking the ejection of lysosomial enzymes with proteinase activity outward and the accumulation of toxic products of the metabolism in the circulation, on one hand, and the disturbance of genetic processes that can control these homeostatic reconstructions, on the other. This substantiates the expediency of antioxidants application in the presence of oxidative stress and allows one to more thoroughly describe the various, slightly studied till now, mechanisms of implementation of a positive influence of these pharmacological substances on the physical workability of athletes. The established facts can become a basis for the development of finer mechanisms of metabolic influence of antioxidants on athletes’ organisms and their ergogenic activity during trainings and competitions.
Conclusions

1. A decrease in athletes’ physical workability is associated with the appearance of oxidative stress, which is revealed by the activation of lipids peroxide oxidation processes with a simultaneous depression of organism intrinsic antioxidative system. The manifestations of oxidative stress on the level of cellular membranes adequately represent the total magnitude of oxidative stress.

2. Antioxidative properties of the studied pharmacological agents of natural origin are coupled with the presence of membranotropic action, which allows one to refer the preparations with such biological effects to ergogenic ones.

3. Violation of a structural-functional state of erythrocytes membranes due to oxidative stress causes a disturbance of their shape and volume, which moderately influences the process of oxygen transport to muscular tissues and, thus, decreases physical workability.

4. Increase in the permeability of cellular and subcellular membranes is accompanied by the ejection of lysosomal proteinases from cells and provokes the process of limited proteolysis, which causes the accumulation of toxic products of uncompleted metabolism and negatively influences the stimulation of the workability.

5. The accumulation of pro-oxidant factors can induce cells apoptosis, which becomes a factor decreasing the physical workability under physical loads.

6. Establishment of the antioxidative action of probiotics creates the additional metabolic preconditions for a growth of the physical workability of athletes.

7. Application of natural antioxidants with metabolotropic character, which has different structures and belongs to different pharmacological classes, is accompanied by stimulation of the physical workability, in the first turn, due to the improvement of a state of cellular and subcellular membranes.

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SANTRAUKA


Raktažodžiai: fizinė veikla, oksidacinius stresas, antioksidacinės medžiagos, struktūrinė ir funkcinė ląstelių membranų būklė, detoksinės savybės, kardiotropinis efektas.

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