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Energy Producing and Apoptosis at Physical Loads: the Role of the Prooxidant-Antioxidant Balance Change (a Review)

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Summary

The article notes that the development of oxidative stress and the violation of cellular energy balance is the primary link of the vast majority of systemically-forming homeostatic shifts in the athlete's body and changes the vital structure and function of cellular and subcellular proteins membrane. Changes in the quantitative and qualitative composition of lipid components of membranes, inhibition of the activity of key glycolysis enzymes, as well as the deterioration of bioenergy mechanisms, result from the accumulation of free radicals due to activation of lipid peroxidation. The protection of the organelles responsible for energy supply from oxidative effects is provided by mitochondrial disconnecting proteins that exist in the myocardium. The development of metabolic ischemia due to the imbalance between the delivery of oxygen to cardiomyocytes and their need for myocardium is accompanied firstly by the inhibition of the process of oxidation of glucose and an increase in the use of fatty acids, and then the accumulation of lactate with the development of acidosis of the intracellular environment and the impairment of the ability of myocytes and cardiomyocytes to relaxtion and contraction. It has been established that strenuous muscle activity leads to the formation of a hypoxic state with its characteristic redistribution and increase of energy, metabolic, structural resources of the body in the interests of the tissue where adaptive adjustments are taking place. The insufficiency of energy generation due to the development of this state leads to the dysfunction of the mitochondrial apparatus, which subsequently causes the violation of the energy supply, antioxidant protection, membrane stability due to intensification of lipid peroxidation and leads to cell apoptosis. This forms a background for the occurrence of fatigue and tension, followed by reduction of physical performance of athletes. The detection of the above changes makes it possible to prevent and correct in a timely manner the negative effects of oxidative stress associated with ultra-intensive physical loads.

Keywords: *physical loads, mitochondria, membranes, energy supply, oxidative stress, apoptosis.*

Introduction

Recently, high efficiency training-competitive activities in connection with the increasing physical loads gained particular relevance in sport (Bezugla et al., 2019), which in different ways affect the internal reaction of the body (Donati et al., 2020). The basis of continuous improvement of physical performance of the athlete is the gradual adaptation of body systems to muscular and emotional pressures. Increase of the amount and intensity of physical loads leads to increased shifts in the functional state of different systems and organs, to the emergence and deepening of fatigue processes, inhibition of recovery processes. According to researchers, physical loads of maximum and submaximal intensity in athletes can cause increased generation of active types of oxygen (ROS – *Reactive Oxigen Species*, which is more often used in the scientific literature) and further development of oxidative stress (OS) (Gomes et al., 2020). Representatives of ROS can be superoxide and hydroperoxide radical, which have toxic and mutagenic effects on all cell types due to oxidative damage to membrane lipids,

proteins and DNA. However, superoxide radicals are very dangerous because they become a source of other forms of ROS, such as: hydrogen peroxide (H_2O_2), hydroxyl radical (HO^-), hypochlorite ($HOCl^-$), ozone (O_3), singlet oxygen (O_2). The intensification of free-radical reactions is a fast-acting mechanism the basic of restructuring energy exchange at the level of the whole organism, and the launch link, which determines the direction of transients processes during phase changes of adaptation during regular physical loads.

In the modern scientific literature, data continue to accumulate on the high biological activity of compounds formed in the reactions of free radical oxidation (FRO) and lipid peroxidation (LP) in the formation of the adaptive response within the physiological response of the body the organism to physical loads (Capó et al., 2020). They are accompanied by significant nervous and mental stress, high energy expenditure in the process of ensuring the contractile activity of muscles. The effectiveness of sports preparation significantly depends on the high functional capacity of skeletal muscles, the capabilities of the lactate and lactate energy systems and the amount of macroergy reserves against the background of increased energy needs of the body. Metabolic acidosis, which occurs during intensive physical work, is due to the accelerated formation of protons in ATPase reactions in the relative insufficiency of aerobic energy formation due to the development the tissue hypoxia of the load (Voitenko et al., 2019).

Inappropriate oxygen saturation of tissues during hypoxia, including hypoxia associated with physical loads, is accompanied by mitochondrial dysfunction, resulting in inhibition of energy-dependent functions and cell exchange. Determining the main links of homeostasis disorders forms an idea of possible directions of prevention and correction of such negative manifestations of long-term effects of high-intensity loads on the athlete's body.

Processes of energy supply under physical loads. With the development of the metabolic direction, it became possible to study in-depth the processes of energy supply. Representations are especially actively formed about the role of disorders of cellular energy during various processes occurring in the body of athletes (Luft, 1994). Energy exchange in cells is carried out by mitochondria – organelles of energy supply, which are the main metabolic processes of the cell, and their functional activity is primarily provides by the inner membrane, which contains components of the electron transport chain (ETC) and reverse H+ – ATPase. The main function of mitochondria is the synthesis of high-energy compounds, which is why they are often called "energy stations" of the cell. The most important for cellular bioenergy reaction of phosphorylation of adenosine diphosphoric acid with the formation of ATP due to the energy of oxidation of organic compounds by molecular oxygen occur in mitochondria (Kondrashova, 1991).

Adenosine triphosphate (ATP) is known to be a universal source of energy in the body and plays a leading role in ensuring the body's vital functions. The additional consumption of ATP makes it possible to replenish the energy resources of the organism, facilitates adaptation to intensive physical loads, thus improving the performance of training and the speed of recovery. However, through a very short half-decay's, there is a problem of the difficulty of delivering ATP to cells in the circulation. At exogenous receipt of ATP under the action of extracellular enzymes it quickly breaks down to adenosine diphosphate, and then to adenosine monophosphate and adenosine. In addition, ATP, like other hydrophilic anions, cannot enter the cell through the plasma membrane (Paggio, 2019).

The flow of protons through the inner mitochondrial membrane is an important mechanism of energy dissipation, which accounts for up to 25% of the basal metabolic rate. It was found that the production of mitochondrial superoxide significantly depends on the protons gradient in isolated mitochondria. Mitochondrial disconnecting proteins can reduce the effectiveness of oxidative phosphorylation and are involved in controlling the production of mitochondrial ROS. Mitochondrial disconnecting proteins that exist in myocardium have been proven to protect mitochondria from oxidative effects, slowing the formation of ATO (Cadenas, 2018).

According to the researchers, oxidative damage to mitochondria contributes to the development of a wide range of pathologies, including cardiovascular, as mitochondrial respiratory chain is an important source of active oxygen species − superoxide and hydrogen peroxide. Under normal conditions at the cellular and subcellular level, the main substrates for energy formation in cardiomyocytes are free

fatty acids, which provide from 60 to 80% of ATP synthesis (mainly by aerobic mechanism), and glucose (20–40% of ATP synthesis − mainly in the aerobic pathway of energy formation) (Frayn, 2003) and support myocardial contractile function. Under the influence of various factors, the type of energy substrate used by cardiomyocytes can change.

It is a known fact that there is a balance between the delivery of oxygen to cardiomyocytes and the need of the myocardium for it, which ensures normal metabolism and, consequently, of heart cells perform their functions. The mitochondria of the myocardium have a certain localization character in the cell, characteristic of the functioning of such an energy-consuming organ as the heart. When the conditions of cell existence change, there are significant modulations in the elements of the cytoskeleton, providing the movement of mitochondria in areas where the diffusion of O_2 is facilitated (Smith, 2011).

As a result of heart vascular damage, there is insufficient blood flow to the heart muscle, which in turn leads to an imbalance between the delivery and the oxygen requirement of the tissues. This in turn causes myocardial perfusion violation with the development of metabolic ischemia. In ischemic myocardium cells, the process of oxidation of glucose is inhibited, while the use of fatty acids is increased. In the absence of oxygen, pyruvate is converted to lactate, because it can not go through all the stages of oxidative decarboxylation in mitochondria. The accumulation of lactate in the cytoplasm consistently leads to acidosis of the intracellular environment and impaired ability of cardiomyocytes to relaxtion and contraction (Gandoy-Fieiras et al., 2020).

The ability of myocardium to oxidize lactate has great biological significance. The use of lactate as an energy source allows you to maintain the required concentration of glucose in the blood longer. Oxidation of lactate in the heart muscle also contributes to the normalization of the acid-alkaline balance, because at the same time the concentration of this acid in the blood is reduced (Ferguson et al., 2018).

It is proved that the cardiovascular system limits the development of adaptive reactions of the body, and the work capacity of the muscle system depends on its state. Increasing the load on the cardiovascular system during intense muscular activity leads to the formation of a hypoxic state, namely, to hypoxia of the load, which is characterized by redistribution and increase of energy, metabolic, structural resources of the body in the interests of the tissue where adaptive changes occur (Bezugla et al., 2017). These restructurings are important because the damage to mitochondria, which are the most sensitive to hypoxia by subcellular organelles, causes violation of energy supply processes, antioxidant protection, membrane stability due to intensification of lipid peroxidation, which can lead to various pathological manifestations (Shing et al., 2011).

The activation of morphogenesis, accompanied by increased energy supply, can contribute to the reduction of hypoxia of the load mitochondria's. Equally important is the increase in the capillarization level of tissues, which improves the blood supply of working muscles, increases the area of gas exchange, slows the rate of blood flow that reduces the path of oxygen diffusion from the blood to mitochondria (Bezugla et al., 2017).

It is known that during the process of adaptation to hypoxia, expands the range of possibilities for adequate provide oxygen to the considerable metabolic needs of muscle tissue under intensive physical loads and compensation – local hypoxia of the muscles, which, under these conditions, is the trigger mechanism for the development of the hypoxia of the load (HL). At the same time, it has been shown that permanent hypoxia of the load can negatively affect the ultra-structure of skeletal muscles (Gavenauskas et al., 2004).

The nature of adaptive readjustments in muscles is largely determined by the intensity of the increase in the amount of load performed. Two types of adaptive hypertrophy in tissues are highlighting, in particular muscle fibres – "rational", connected with an increase in the number of structures providing a reinforcing function and "irrational", characterized by a high rate of increase in the volume of the executable loads, as a result, a program is enabled to rapidly increase the functional capacity of the organism. Implementation of similar program takes place under conditions of energy shortage and is carried out mainly by increasing the size of organoids of the cell. Energy supply the muscle work is provided mainly by three ways of ATP resynthesis: creatin phosphated (alactate), glycolytic (lactate) and aerobic (tissue respiration). Depending on the dominance of one or another pathway of ATP resynthesis in the energy supply of the work

performed, there are three components of working capacity: alactate capacity, lactate capacity and aerobic capacity (Ferguson et al., 2018).

Under the oxygen deficiency conditions, the main part of aerobic ATP synthesis is accounted for by β-oxidation of higher fatty acids (HFA), which in conditions of ischemia requires the high expenses of oxygen. Due to the hypoxic (and then ischemic) state of any genesis leads to the formation of excess HFA and acetyl CoA, which suppress the functioning of the pyruvate dehydrogenase complex, and leads to further separation of the glycolysis and oxidative decarboxylation processes, as well as to activation FRO (Gandoy-Fieiras et al., 2020). As a result, it increases in the formation of ROS, which can damage lipids of membrane (lipid peroxidation) with the emergence of oxidative stress; there are additional damages to functionally important proteins, in particular the cytochrome respiratory chain and myoglobin, nucleic acids and other structures and molecules included in cardiomyocytes. Cellular acidosis, local inflammation, peroxidation, and reduction of ATP synthesis are at the root of the development of electrophysiological and functional dysfunction of myocardium (Randle et al., 1963).

Lipid peroxidation and antioxidant protection under physical loads. Despite numerous studies showing that the uncontrolled and excessive production of LP products during OS is a main cause of various pathological conditions and diseases, the mechanisms by which lipid peroxidation products regulate oxidative, immune and inflammatory reactions remain undetermined. This process is the primary link of the vast majority of homeostatic shifts in the body and can change the vital structure and function of membrane proteins, both cellular and subcellular (lysosomes, mitochondria, ribosomes, etc.) (Ramana et al., 2017), because during its activation violate the quantitative and qualitative composition of lipid components which worsens their structural and functional state. Lipid peroxidation is a complex chain reaction process that is realized through ATO-mediated attacks on cell membrane lipid radicals, primarily polyunsaturated fatty acids (PUFA), which leads to cell damage and dysfunction. As a result of the oxidation of fatty acids, hydroperoxides (diene conjugates) are formed, which are subsequently metabolized to the secondary malondialdehyde (MDA) and tertiary products of lipid peroxidation (chiffa bases). The end products of LP give a significant amount of highly reactive electrophilic aldehydes, which can act as endogenous danger signals (messengers), changing the important paths of cell signals transmission responsible for the emergence of numerous pathological conditions (Kowalczuk, Stryjecka-Zimmer, 2002).

At the same time, these processes are the most importent and significant in the adaptive updating and reparation of functioning structures, lipoprotein membranes, increased power and buffer capacity of the redox system. It's not only a pathophysiological process, but also a physiological process that constantly occurs in biological membranes and participates in the important function of cell membranes renewal, in the biosynthesis of many biologically active substances, the conducting of nerve impulse and is a necessary chain of oxidative phosphorylation (OP) in mitochondria (Onasanwo, Rotu, 2016).

According to the opinion that was formed earlier, and does not objection now by the vast majority of domestic and foreign researchers, maintaining a high level of adaptation to the maximum and submaximum physical loads that accompany training and competitive activities leads to a significant activation of LP processes (Gunina, 2015), accumulation of free radicals, which in turn contributes to the formation of toxic metabolic products that violate the structure and function of cell membranes and lead to deterioration of bioenergy mechanisms and, respectively, the reduction of physical performance. It has been proven that a large number of toxic LP products can inhibit the activity of key glycolysis enzymes, as well as important enzymes such as RNA-azes, succinate dehydrogenase, acetylcholinesterase and others, which can adversely affect athlete's physical performance.

The intensity of LP processes can increase in untrained humans and animals, even under the influence of single-use physical loads of low power, which for them are stressful. Intense physical loads and its inherent various metabolic shifts are accompanied by negative changes in antioxidant protection (Adlam, 2005). Activation of the LP while simultaneously inhibiting the activity of its own (endogenous) antioxidant system, that constantly accompanies training process of qualified athletes can lead not only to a significant

increase in the "price of adaptation", but also to shift the entire system of adaptation capabilities of the body, to violating adaptive mechanisms and, as a consequence, to the development of fatigue and reduced physical performance (Fig. 1).

Excessive formation of highly active ROS is the initial stage of development of this process. Free radicals (oxidants) are unstable, chemically active compounds formed by the use of oxygen "fuel" in cells. Their instability is predefined to the unbalanced number of electrons relative to the value of the charge of the nucleus. Such unbalanced molecules try to recover by giving up their extra electron or tear off the missing one from another molecule. In turn, the other molecule becomes unbalanced in the number of electrons and seeks for balance, continuing the reaction. In small amounts, free radicals play a useful role in maintaining health by participating in many chemical reactions that constantly occur in cells. However, the effect of intense physical load leads to violations of natural controls mechanisms, and then free radicals' activity increases sharply, destroying structural units of tissues, organs and the body as a whole. Oxidative stress reflects an imbalance between the production of active oxygen species and adequate antioxidant protection. When insufficient power of ROS own antioxidant system destroy cells, damaging cell and subcellular membranes, causing mutations, change DNA structure (Fischer et al., 2018).

It is known that ROS play a role in cell metabolism, for example, superoxide radical and hydrogen peroxide are messengers, in some pathways of signaling induction and required in protective reactions, in conducting a danger signal, in the disposal of toxic substances, which accumulate during motor activity. Therefore, the formation of ROS must be controlled, and the role of the controllers is played by antioxidant systems (Capó et al., 2020). There are two levels of the antioxidant system in the body. The first of them is not enzymatic, which is determined by the presence of antioxidants and reductant in the tissues of the body, which inhibit the development of POL processes. The enzymatic antioxidant system has an important role in protecting the organism under intense physical loads, when the active oxygen forms, which are also defined as ROS (see above), accumulate in very large quantities, especially during training of considerable duration and intensity (Li et al., 2016).

Reactive oxygen species are formed by living cells as a normal cellular metabolic by-product. Under excessive oxidative stress, cells produce numerous ROS, and living organisms over time develop a number of response mechanisms to adapt to the effects of ROS, as well as use them as signal molecules. ROS molecules cause oxidative stress in the feedback mechanism, which includes many physiological processes such as apoptosis, necrosis and autophagy (Cadenas, 2018).

It should be added that apoptosis and necrosis are the two main ways of programmed cell death, the molecular mechanisms of which have been widely studied. Although they were initially thought to constitute mutually exclusive cellular states, recent research findings reveal cell contexts that require a balanced interaction between these two methods of cellular death. Several molecules of cell death initiator and effector molecules, signaling pathways and subcellular sites have been identified as key mediators in both processes or constituting common modules, or alternatively functioning as that allows cells to decide which path to take, depending on the situation (Wang, 2015). It is important that autophagy, which is a predominantly cytoprotective process, is associated with both types of cell death, serving or function of life or death (Packer, 2020). ROS plays an important role in all three processes, and intensive long-term physical activity is no exception. Therefore, in such system-forming processes as apoptosis and necrosis, which constantly occur in the body and are exacerbated during training and competitive loads, ROS play an important role. And this in sports biochemistry and pharmacology cannot but be one of an important aspect of the studying of the subtle mechanisms of the corrective effect of antioxidant factors on the athlete's body and his physical fitness (Zhou et al., 2019).

ROS play a crucial role as signaling molecules throughout the path of cell death. Overtime production of ROS can destroy the structure of organelles and biomolecules, which leads to an inflammatory reaction, which is a known basis for the mechanism of development of a significant number of pathophysiological conditions (oncological diseases, peptic ulcer disease, chronic obstructive pulmonary diseases, diabetes, in sports − overtraining). Cytochrome P450 (CYP) enzymes, considered as markers of oxidative stress,

can convert toxic metabolites to ROS, such as superoxide anion, hydrogen peroxide, and hydroxyl radical, which can cause cell damage. Accordingly, there is a balanced system in cells to neutralize excess ROS, namely antioxidant systems consisting of enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), thioredoxin (Trx), nonenzymatic antioxidants which together able reduce the severity of the oxidative state (Jones, 2008).

Substances known as antioxidants play a crucial role in preventing and controlling negative metabolic shifts in the body, acting as neutralizers of free radicals. Antioxidants are compounds that have an excess of "free electrons" that bind to free radicals and do not cause a chain reaction. They help neutralize the negative effects of lipoperoxidation in the body of athletes during long and intensive physical loads (Dmitriev, Gunina, 2020).

The results of numerous studies in recent years have proven that the main areas of their influence in the cell of the body are membranes and the nuclear genome. By embedding in cell membranes, antioxidants become effective inhibitors of free radical chain reactions. Lack of membranotropic antioxidants in the body leads to irreversible damages of membranes by LP products, which causes occurrence of pathological states, reduced life expectancy and in some cases – the death of the organism. The imbalance between LP activity and the power of the antioxidant protection system (AOP) results in an avalanche-like of peroxidation reaction, which leads to cell death – cytolysis (Feysa, 2019). Dysfunction of the antioxidant system occurs both with insufficient entrance of antioxidants and with their excessive amount. Regulation of the constancy of the concentration of lipid peroxides in biological membranes is carried out largely due to the balanced interaction of the reactions of formation of these products (oxidation reactions) and control mechanisms that lead to inhibition of their formation (antioxidant reactions).

Thus, the issue of the correction of the energy shortage and the possibility of directly influencing the state of the antioxidant system by the use of endogenous substances in order to increase the effectiveness of training and competitive activities is very relevant, as well as speeding the processes of energy supply and rehabilitation of athletes, engaged physical loads of maximum intensity, with the need to eliminate the negative effects of the impact on the main metabolic processes in the cells of the organism and maintain a high level of functional preparedness for a sufficiently long of time.

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ENERGIJOS GAMYBA IR APOPTOZĖ FIZINIO KRŪVIO METU: KAIP KEIČIASI PROOKSIDANTŲ IR ANTIOKSIDANTŲ PUSIAUSVYRA (APŽVALGA)

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SANTRAUKA

Straipsnyje teigiama, kad oksidacinio streso vystymasis ir ląstelių energetikos sutrikimas yra pirminės daugelio sisteminių homeostazės pokyčių sportininkų organizme priežastys, dėl kurių kinta gyvybiškai svarbių ląstelių ir subląstelinių membranų baltymų struktūra ir funkcijos.

Kiekybiniai ir kokybiniai membranų lipidinių komponentų sudėties pokyčiai, pagrindinių glikolizės fermentų slopininmas ir bioenergetinių mechanizmų veiklos silpnėjimas atsiranda dėl laisvųjų radikalų susikaupimo, kurį lemia riebalų oksidacija. Ląstelių, atsakingų už energijos aprūpinimą, apsaugą nuo oksidacinio poveikio atlieka baltymai, esantys širdies miokardo mitochondrijose. Metabolinės išemijos vystymasis, atsirandantis dėl sutrikusios kardiomiocitų aprūpinimo deguonimi ir jo poreikio pusiausvyros, pirmiausia pasireiškia glikolizės oksidacijos proceso slopinimu ir riebalų rūgščių vartojimo padidėjimu, o po to ir laktato susikaupimu, acidozės didėjimu ląstelėse bei sumažėjusiu miocitų ir kardiomiocitų susitraukimo ir atsipalaidavimo gebėjimu.

Nustatyta, kad intensyvus fizinis krūvis sukelia hipoksiją su jai būdingais požymiais – energetinių, metabolinių, struktūrinių organizmo resursų persiskirstymu audiniams, kuriuose vyksta intensyvus adaptacinis prisitaikymas. Nepakankama energijos gamyba, atsiradusi dėl šio situacijos, sukelia mitochondrijų disfunkciją ir dėl to sutrikdo aprūpinimą energija, antioksidacinę apsaugą, membranų stabilumą ir galiausiai pasireiškia ląsteliu apoptoze. Tai sudaro prielaidas pervargti ir persitempti, sumažina sportininkų fizinį darbingumą.

Minėtų pokyčių išaiškinimas leidžia laiku diagnozuoti ir koreguoti neigiamus oksidacinio streso organizme padarinius atliekant didelio intensyvumo fizinius krūvius.

Raktažodžiai: fizinis krūvis, mitochondrijos membranos, energetinis aprūpinimas, oksidacinis stresas, apoptozė.

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