DOI: 10.34287/MMT.4(59).2023.10
Огляд літератури / Reviews of literature
UDC 615.272.015:613.71/.73:796

Use of metabolites, metabolithotropic agents and nutritional supplements in sports and sports medicine: a modern view on the problem

I. F. Bielenichev*[1,A,C,D,F], N. A. Gorchakova[2,B,E], E. Yu. Doroshenko[1,B,E], I. B. Samura[1,B,D], V. P. Ryzhenko[1,B,D], N. V. Bukhtiiarova[1,B,E]

[1]Zaporizhzhia State Medical and Pharmaceutical University, Ukraine, [2]Bogomolets National Medical University, Kyiv, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Key words:
sports, sport training, metabolite agents, metabolitotropic drugs, nutritional supplements.

Ключові слова:
спорт, тренувальний процес, метаболітні препарати, метаболітотропні препарати, харчові добавки.

Надійшла до редакції / Received: 31.07.2023

Після доопрацювання / Revised: 12.09.2023

Схвалено до друку / Accepted: 20.09.2023

Конфлікт інтересів:
відсутній.

Conflicts of interest:
authors have no conflict of interest to declare.

***E-mail:**
i.belenichev1914@gmail.com

Aim. The purpose of this study was to conduct an up-to-date semantic analysis of the results of our own research and literature data on the medical and pharmacological characteristics of metabolites, metabolitotropic agents and nutritional supplements, the peculiarities of their use in sports practice and sports medicine.

Materials and methods. This study used bibliosemantic, analytical, logical, and generalization methods. The life sciences and biomedical information bibliographic databases MEDLINE, EMBASE, Medline (PubMed), Web of Science, and Cochrane Central were searched to find publications in English that matched the research keywords. The authors carried out an independent search and selection of articles, assessment of the quality of the data, compliance of the presentation and interpretation with the main idea of the study, with the formation of the final list of references.

Results. Based on the analysis of modern literature data and the results of our own studies, a generalized medical and pharmacological characteristic of metabolite agents, metabolitotropic drugs and nutritional supplements that can influence the main and compensatory mechanisms of macroergic phosphates production under the influence of physical activity is presented. The mechanisms of action, indications for use and main side effects of drugs and food additives based on ATP, malate, succinate, citrate, pyruvate, carnitine, carnosine, etc. are presented.

Conclusions. Semantic analysis data indicate that an urgent problem for sports medicine physicians and pharmacologists is the development and use of metabolites, metabolitotropic agents and nutritional supplements, as well as approaches to their rational combination to improve energy metabolism, replenish ATP reserves in the body that will help ensure the intensity muscular activity and simultaneously protect target organs.

Modern medical technology. 2023;(4):76-88

Застосування метаболітних, метаболітотропних препаратів і харчових добавок у спорті та спортивній медицині: сучасний погляд на проблему

І. Ф. Бєленічев, Н. А. Горчакова, Е. Ю. Дорошенко, І. Б. Самура, В. П. Риженко, Н. В. Бухтіярова

Мета роботи – надати актуальний семантичний аналіз результатів власних досліджень і відомостей фахової літератури щодо медико-фармакологічних характеристик метаболітних, метаболітотропних фармакологічних препаратів і харчових добавок, а також особливостей їх використання у спортивній медицині.

Матеріали та методи. Під час дослідження використали бібліосемантичний, аналітичний, логічний методи, а також метод узагальнення. У бібліографічних базах даних наук про життя та біомедичної інформації MEDLINE, EMBASE, Medline (PubMed), Web of Science і Cochrane Central здійснили пошук англомовних публікацій, що відповідають ключовим словам дослідження. Здійснили самостійний пошук і відбір статей, оцінювання якості даних, відповідності викладу та інтерпретації основній ідеї дослідження, сформували остаточний список літератури.

Результати. На основі аналізу відомостей сучасної фахової літератури, а також власних досліджень дали фармакологічну характеристику метаболітним, метаболітотропним препаратам і харчовим добавкам, що можуть впливати на основні механізми та компенсаторні шунти продукції макроергічних фосфатів під час тренувального процесу та фізичних навантажень. Наведено механізми дії, показання до застосування й основні побічні ефекти препаратів і харчових добавок на основі АТФ, малату, сукцинату, цитрату, пірувату, карнітину, карнозину тощо.

Висновки. Зважаючи на результати семантичного аналізу, актуальним завданням для спортивного лікаря та фармаколога є розроблення метаболітотропних препаратів і харчових добавок, а також підходів до їх раціонального комбінування для покращення енергетичного обміну, поповнення запасів АТФ в організмі, що сприятиме забезпеченню інтенсивності м'язових скорочень та одночасному захисту органів-мішеней.

Сучасні медичні технології. 2023. № 4(59). С. 76-88

An urgent problem of modern sports science is the development and use of adequate pharmacological support to ensure and increase the parameters of the physical performance of athletes, accelerate the processes of adaptation of their body to high-intensity physical activity, prevent overtraining and sports injuries. In this context, pharmacological support of sports activity is a correction of functional adaptation capabilities, allowing to expand the body's ability to adapt to the maximum loads of high-performance sports [1]. The rational use of pharmacological and non-pharmacological agents in various periods of the training and competitive process contributes to the achievement of the highest possible sports results [2].

Currently, in the practice of pharmacological support of sports activities, two groups of non-doping pharmacological agents and food additives are widely used. These are pharmacological and non-pharmacological agents necessary for the rehabilitation of athletes after overtraining or illness, and agents that enhance the adaptation of athletes to physical activity (accelerate the recovery process and increase physical performance) [3].

The development of sports pharmacology has put experts before choosing a huge number of agents and nutritional supplements with various chemical structures, different (sometimes insufficiently known) mechanisms of action and unidentified adverse reactions [4]. All of the above can not only reduce the effectiveness of sports training, but also harm the health of the athlete.

Aim

This study aims to conduct an up-to-date semantic analysis of the results of our own research and literature data on the medical and pharmacological characteristics of metabolites, metabolitotropic agents and nutritional supplements, the features of their use in sports practice and sports medicine.

Materials and methods

This study used bibliosemantic, analytical, logical, and generalization methods. The life sciences and biomedical information bibliographic databases MEDLINE, EMBASE, Medline (PubMed), Web of Science, and Cochrane Central were searched to find publications in English that matched the research keywords.

The authors carried out an independent search and selection of articles, assessment of the quality of the data, compliance of the presentation and interpretation with the main idea of the study, with the formation of the final list of references [5].

Results

The main principles of pharmacological support of sports training are as follows:

– acceleration of recovery processes after training and competitive loads should be achieved by creating optimal conditions (including with the help of pharmacological agents) for their natural course;

– when prescribing pharmacological medicines, it is necessary to understand the purpose for which they are used, mechanisms of their action and, on this basis, determine the nature of their influence on the effectiveness of the training process, as well as contraindications for use, possible complications, and the results of the interaction of some agents with others;

– taking into account urgent, remote and cumulative effects of pharmacological agents;

– differentiated influence on the parameters of physical performance: power, capacity, efficiency, mobilization and implementation;

– the degree of efficiency depending on the qualification level, the initial functional state of the body, the period of the training cycle, the energy nature of the current training and upcoming competitive loads [6,7].

Based on the above principles, the following variant of the classification of metabolite and metabolitotropic pharmacological agents, and nutritional supplements used in the practice of pharmacological support of sports training is proposed [8]:

1. Agents providing increased demands of the body in the main food ingredients (vitamins, amino acids, etc.) under conditions of intense muscular activity [9];

2. Artificially stimulating recovery processes after significant physical exertion by accelerating the excretion and binding of metabolic products (medicines that improve renal blood flow, amino acids, metabolites, hepatoprotectors) [10];

3. Improving adaptation to training and competitive loads due to:

– reducing the formation of toxic metabolites (antioxidants) during intense muscle activity [11];

– decreasing the injuring effect of these metabolites (antihypoxants and metabolites of plastic metabolism) [12];

– preservation and urgent restoration of ATP reserves (substrates and metabolites of energy metabolism, macroergs, antihypoxants, mitoprotectors);

– activation of stress-limiting systems (amino acids, antioxidants, regulators of transcription factors) [13].

Below is a brief description and the main mechanisms of action of these drugs.

Adenyl nucleotides are high-energy compounds that act as carriers of ATP phosphoryl groups, which is necessary for various reactions, including the synthesis of proteins and nucleic acids, and which serves as an energy source during muscle fiber contraction, and ensures the work of transmembrane ion pumps. The therapeutic efficacy of ATP is a result of its direct effect on purine receptors. ATP also takes part in the processes of neuromuscular transmission of impulses, acting as a modulator of synaptic transmission. At the same time, negative myotropic and chronotropic effects of adenosine and stimulation of glycogenolysis in the myocardium are the main factors that protect the myocardium from damage during intense muscle activity [14].

ATP-long is an original agent, a coordination compound used for optimization of the training process of highly qualified athletes [15]. The drug was synthesized in such a way that the macroergic phosphate, the amino acid histidine, magnesium and potassium salts included in its composition are coordinated, and its molecules are easily integrated into various metabolic processes due to structural similarity with cell membrane receptors. ATP-long produces the following pharmacological effects:

– cardioprotective action under conditions of ischemia and working hypoxia;

– increase of energy resources at the cellular level;

– inhibition of oxidative stress;

– increase in activity of ion transport systems, Na^+/K^+- and Ca^{2+}-ATP-ases, and calcium-binding potential of cell membranes;

- normalization of potassium and magnesium levels in the myocardium;

– improvement of indicators of central and peripheral hemodynamics, coronary blood flow;

– optimization of the left ventricle functional state under conditions of ischemia and increased myocardial oxygen consumption [15].

The ergogenic properties of nutritional supplements containing ATP are manifested exclusively with a course intake, starting with a dose of 400 mg per day, and in combination with constant strength training loads. ATP in a single oral dose in the dose range of 150–225 mg/day has a weak ergogenic effect in the development of strength abilities. Dietary supplementation of ATP at a dose of 400 mg daily for 15 days has been shown to reduce muscle fatigue and increase performance in repetitive exhaustive exercise cycles by improving low-intensity movement performance. This can lead to an increase in the overall level of physical fitness. The ergogenic effect of a 12-week-long intake of ATP at a dose of 400 mg/day in combination with high-intensity regular power loads is universal: an increase in the strength abilities and power of skeletal muscles (from 30 % and above); hypertrophy of muscle fibers; inhibition of protein breakdown under the influence of physical activity; reduction of subjective feeling of fatigue at later stages of stress factor action; increased post-exercise blood flow to skeletal muscle, which may be responsible for reducing muscle fatigue and preventing loss of muscle strength during repeated cycles of high-intensity exercise [16].

In the initial (early) stages of physical activity, ATP dietary supplements have the potential to increase muscle excitability, and in the later stages (at the end of the loading period) to prevent its decrease [17]. Such properties of the oral form of ATP may be of the greatest practical importance in team sports (for example, basketball, football, hockey, etc.). The use of high doses of ATP in course use for a period of 14 days to 12 weeks is not only effective, but also safe.

The ergogenic effect of taking ATP food supplements develops not because of an increase in blood ATP levels due to an external source, but due to the inclusion and progressive increase in the synthesis of endogenous ATP as a response to biochemical signals from receptors on the outer surface of cell membranes. Such a signaling mechanism for stimulating endogenous ATP synthesis is polymodal and, theoretically, may include the following [18]:

1. "Gut-muscle axis" known in the scientific literature (gut-skeletal muscle axis) – the concept in which the processes occurring in the intestine activate/inhibit tissue metabolic processes in a neurohumoral way, including energy ones in muscle fibers;

2. Activation of purinergic receptors on the membrane of muscle cells by ATP metabolites, stimulation of intracellular processes of nucleotide synthesis, acceleration of anabolic reactions during the course intake of ATP. The implementation of these trigger mechanisms occurs only under conditions of intense physical activity with all the accompanying physiological and biochemical changes in the body (hypoxia, sensitization of a number of receptor processes, etc.).

The universal character of the ergogenic action of dietary ATP supplements has served as the basis for the creation of combined forms of ATP with other pharmacological nutrients, such as beta-hydroxy-beta-methylbutyrate (HMB) and its free acid form (HMB-FA); leucine, isoleucine and valine (2:1:1); L-carnitine and electrolytes to enhance ergogenic properties. The combination of ATP with HMB has the highest degree of evidence [19].

The combined use of HMB-FA (3 g/day) and ATP (400 mg/day) for 12 weeks in high-class athletes in combination with systemic strength training has a pronounced anabolic effect, improves strength and power of skeletal muscles. These effects are complemented by the ability of this combination to prevent muscle strength decline and even ensure its further growth under conditions of extreme physical cyclic loads. The ergogenic properties of the combination of HMB-FA and ATP can be used in the training and competitive activities of professional athletes.

ATP-propionyl-L-carnitine. Food supplement based on L-carnitine derivative (propionyl-L-carnitine – PLC) and ATP. Biochemical studies have shown that PLC increases the levels of ATP in the body, including in the myocardium [20]. It is recommended to take one capsule twice daily on an empty stomach. At the same time, as noted above, the effective dose of ATP is at least 400 mg per day, which should be taken into account by sports medicine physicians and coaches.

Ready forms of ATP with electrolytes. AIM Peak Endurance® commercial ready-to-use blend is based on the same form of ATP, PEAK ATP®. The finished mixture contains, in addition to 200 mg of ATP, the main electrolytes (sodium, potassium, chlorine, calcium, magnesium, phosphorus) with the addition of vitamins C and group B: B_1, B_2, B_3, B_5, B_6 and B_{12}. Thus, two recommended servings of AIM Peak Endurance® per day provide 400 mg of ATP required for ergogenic action in combination with essential minerals and vitamins. Magnesium is a key component of more than 300 enzymes including ATPase and enzymes involved in the metabolism of muscle glucose and glycogenesis [7].

Magnesium ions, a natural antagonist of calcium ions, provide a negative inotropic effect on the myocardium, thereby reducing its oxygen consumption; reduce peripheral resistance by reducing the tone of smooth muscle structures of blood vessels. Magnesium also inhibits the processes of deamination and dephosphorylation. Potassium ions maintain osmotic and acid-base homeostasis of cells, take part in providing a transmembrane potential (electrical gradient), and activate the synthesis of ATP and creatine phosphate. This powder composition meets the modern requirement for polyionic solutions to compensate for the loss of water and electrolytes (compensation not only for sodium, potassium and chlorine) in the training and competitive process.

It is recommended to take one rounded scoop (8.33 g) of the mixture, diluted in 100–200 ml of water, twice daily, on an empty stomach and before meals. The standard dose of 300 g of the mixture (*package*) after dilution gives an average of 21 liters of the finished drink.

Phosphocreatine (Creatine phosphate, Neoton), the phosphorylated form of creatine, is a key substrate in the system of macroergic compounds transport to their disposal sites, where it plays a critical role as a rapidly acting energy buffer for muscle cell actions like contractions via its ability to regenerate ATP from ADP. Phosphocreatine improves myocardial energy metabolism, intracellular energy transport, and inhibits the destruction of the sarcolemma of ischemic cardiomyocytes [18]. Phosphocreatine stimulates microcirculation, reduces the size, and prevents the expansion of the zone of necrosis and ischemia. Under conditions of ischemia and postischemic reperfusion injury, Neoton exhibits an antiarrhythmic effect: it suppresses the ectopic activity of the ventricles without disturbing the conduction of the Purkinje fibers.

Biochemical mechanisms of phosphocreatine action [21] include:

1. Inhibition of platelet aggregation by removing ADP during the extracellular creatine kinase reaction;

2. Phosphocreatine penetration of into cells and participation in the energy transport system by maintaining high local concentrations of ATP;

3. Inhibition of adenyl nucleotides degradation at the level of the 5-nucleotidase reaction occurring in the sarcolemmal membrane of cardiomyocytes;

4. Inhibition of the accumulation of lysophosphoglycerides in the myocardium during physical exertion and ensuring the safety of the structure of the sarcolemma of myocardiocytes;

5. Protection of cardiomyocytes membranes and skeletal muscle cells because of electrostatic interaction between the drug molecule and phospholipids in the presence of Ca^{2+}.

In sports medicine, phosphocreatine is used to prevent the development of overtraining syndrome and improve adaptation to extreme physical exertion, as well as an effective cardioprotector for hypoxic and metabolic myocardial disorders. To prevent the overtraining syndrome and improve adaptation to extreme physical conditions, phosphocreatine is administered at doses of 1–8 g in 200 ml of saline or 5 % glucose solution.

Creatine. According to the modern concept, creatine belongs, on the one hand, to the group of myostatin inhibitors, and on the other hand, to protectors of mitochondrial function. Myostatin is an extracellular cytokine most abundant in skeletal muscle which plays a critical role in negative regulation of skeletal muscle mass by inhibiting skeletal muscle cells growth and differentiation. Increasing muscle creatine through creatine supplementation may increase the availability of phosphocreatine and accelerate the rate of ATP resynthesis during and after high-intensity short training sessions. In 2007, the nine main points were formulated regarding the use of creatine supplements in sports [7]:

1. Creatine monohydrate (CM) is the most effective ergogenic supplement available to athletes in terms of increasing their ability to tolerate high intensity training and increase body weight;

2. CM has a high safety profile for an athlete with long-term use;

3. CM can serve as an alternative (with precautions and medical supervision) to potentially dangerous and prohibited by WADA steroidal drugs;

4. CM is currently the most extensively studied and clinically effective form of creatine for use as a dietary supplement to increase muscle strength and exercise capacity;

5. When combined with carbohydrates or carbohydrate / protein supplements, CM promotes creatine retention in the muscles, although the overall effect on fitness with such combinations may not be greater than the use of CM alone [17];

6. The fastest way to increase muscle creatine stores is to take a loading dose of CM of approximately 0.3 g/kg/day for 3 days followed by a maintenance (of muscle creatine stores) dose of 3–5 g per day. Taking smaller doses of CM (2–3 g/day) will take approximately 3–4 weeks to increase muscle creatine depot, but this regimen has less support in the scientific community;

7. Products containing creatine are available as dietary supplements and are regulated by the FDA (USA). The special law of 1994 (the Dietary Supplement Health and Education Act, DSHEA) prohibits listing specific diseases or syndromes as indications for nutritional supplements;

8. CM, as noted in several publications, has a positive effect in some clinical situations that is a separate scientific direction and requires special research.

In addition to CM, there are other nutritional supplements based on creatine such as creatine pyruvate; creatine citrate; creatine malate, creatine phosphate, and creatine orotate, as well as other combined formulations: Creatine + HMB; Creatine + Sodium bicarbonate; Chelate compound of creatine with Magnesium; Creatine + Glycerol; Creatine + Glutamine; Creatine + beta-alanine; Creatine ethyl ester; Creatine + Cinnuline extract.

Riboxin. The active substance is the purine nucleoside inosine, part of the RNA macromolecules that deliver oxygen to muscle cells, participates in the formation of ATP molecules, which provide energy for intracellular processes, including the contraction of muscle fibers. Due to the ability to increase ATP synthesis, inosine exhibits anti-ischemic, cardioprotective and actoprotective properties. The drug normalizes the heart rate, improves the oxygen regime of myocardial tissues, increases the force of heart contractions, stroke volume of blood, optimizes the cardiac cycle; activates the metabolism in heart tissues, accelerates their regeneration and reduces the risk of blood clots by reducing platelet aggregation [22].

The anabolic properties of riboxin are used to train athletes in the group of strength sports: weightlifting, powerlifting, bodybuilding etc. [23]. Riboxin promotes an increase in the ratio of "protein – free amino acids" and the inclusion of amino acids in protein synthesis. Riboxin doesn't exhibit steroid hormone properties, it has an immunomodulating effect, increases interferon synthesis, positively affects tissue regeneration, accelerates wound healing, and reduces the expression of pro-inflammatory cytokines and mediators. In the training process in power sports, riboxin not only helps to increase muscle mass, but also protects the heart of athletes from overload, showing cardioprotective properties. The recommended daily dose of Riboxin is from 0.6 g (1 tablet 0.2 g thrice a day) to 2.4 g (4 tablets 0.2 g thrice a day), depending on the purpose. For cardioprotection during intensive training, 0.8 g/day (0.2 g 4 times a day) is administered. For a noticeable anabolic effect, accelerating the growth of strength abilities and muscle mass, riboxin is administered at a dose of up to 0.2–0.3 g per 10 kg of athlete's body weight. In this case, the dose is increased stepwise: 0.2 g added to each dose every 2–3 days.

Energostim is a metabolitotropic drug, which includes nicotinamide dinucleotide, cytochrome-C and inosine, which increase the contractile activity of the myocardium and prevent the development of metabolic disorders in toxic-allergic myocarditis. Energostim is used orally in tablets 600–800 mg/day or parenterally. If the drug is well tolerated, the dose is gradually increased over 2–3 days: first to 1.2 g/day (2 tablets thrice a day), then to 2.4 g/day (4 tablets thrice a day). Energostim can be given by intravenously either as a bolus or infusion (40–60 drops/min): initially 200 mg (10 ml of 2 % solution) once a day, then, if well tolerated, up to 400 mg 1–2 times a day. Intravenous (IV) injection of 200–400 mg in a single dose (10–20 ml of a 2 % solution) may be used for arrhythmias. Energostim is diluted for IV infusion in 5 % glucose solution or in isotonic sodium chloride solution.

L-carnitine, refers to agents with anabolic action, acts as the main cofactor in the metabolism of fatty acids in the myocardium, liver and skeletal muscles, plays the role of the main transporter of fatty acids into mitochondria, where they are beta-oxidized to acetyl-CoA, which is a substrate for ATP formation in the Krebs cycle [9]. L-carnitine promotes the release of metabolites and toxic substances from the cytoplasm, improves metabolic processes, increases efficiency, appetite, accelerates growth, causes weight gain, reduces the functional activity of the thyroid gland, and contributes to the normalization of basal metabolism in hyperthyroidism [24].

L-carnitine reduces the symptoms of physical and mental overstrain, produces neuro-, hepato- and cardioprotective action, lowers cholesterol levels, slows down the formation of vascular atherosclerotic plaques, helps to reduce myocardial ischemia and limit the post-infarction zone, stimulates cellular immunity, eliminates functional disorders of the nervous system in patients with chronic alcoholism and neurological diseases [25]. Carnitine produces actoprotective action by stimulating the use of fats for energy production, reducing the rate of glycogen consumption in muscles, activating the use of glucose in muscles as an energy substrate with simultaneous decline of lactic acidosis, reducing muscle fatigue and increasing endurance [15]. The optimal recommendation for carnitine is 0.5–2.0 g/day (the usual single dose is 500 mg or 750 mg thrice a day, or 1000 mg twice a day). There is no point in exceeding 2 g, as studies have not shown any benefit of higher doses. L-carnitine is taken in the morning on an empty stomach and 30 min before training. On days free from training, the drug is also taken in the morning and afternoon between meals on an empty stomach, because L-carnitine is most active in the morning hours and during physical activity.

L-lysine is an essential amino acid that takes part in all processes of assimilation and growth, promotes ossification and growth of bone tissue, stimulates cell mitosis, and supports female sexual function. L-lysine increases the affinity of inhibitory GABA receptors and has anticonvulsant, anxiolytic, neuroprotective, and stress-protective properties. L-lysine normalizes the "eNOS – iNOS" ratio and promotes endothelial protection [26], improves microcirculation and has capillary protective action, accelerates recovery processes in muscles after strength training. The modulating effect of lysine supports a positive nitrogen metabolism and the structure of muscle proteins. Muscle protection and nutrition are the two main functions of lysine in athletic training [27]. In addition, lysine strengthens the tendon corset and the skeletal system, which reduces the risk of sports injuries and speeds recovery. Dosage: up to 1000 mg per day with meals.

Taurine, a naturally occurring sulfur-containing amino acid, called a "miracle molecule", particularly concentrated in the brain, heart, eyes, and muscles, promotes axonal growth and transport, improves the transmission of nerve impulses in synapses Taurine is known to have an antioxidant effect, it inhibits the processes of peroxidation and oxidative modification of proteins during exercise, and improves cognitive functions – memory, mental activity, attention, orientation, concentration, and visuospatial skills; and accelerates the reduction of neurological disorders [28]. Taurine significantly reduces hormonal and metabolic disorders during stress and exercise [29,30]; exhibits hepatoprotective properties, improves the detoxifying functions of the liver; regulates atrioventricular conduction, reduces the refractory period of the myocardium, and normalizes cardiac hemodynamics parameters during exercise [31]. In sports nutrition, the common dosage range for taurine is 400–1000 mg.

Glutamic acid is actively involved in energy, protein, and fat metabolism. The protective effect of glutamic acid is based on its influence on biosynthetic processes and an increase in muscle mass. The antihypoxic effect of glutamic acid is realized primarily at the level of energy homeostasis and changes in the metabolic properties of mitochondria [18].

Glutamic acid is actively involved in the regulation of energy metabolism since it can serve as a source of succinic acid under hypoxic conditions and trigger oxidative phosphorylation. The preventive effect of glutamic acid under hypoxic conditions is also associated with an increase in the concentration of α-ketoglutaric acid, followed by the accumulation of oxalic acid in tissues, which creates conditions for the lactate and other underoxidized metabolic products participation in the Krebs cycle.

The use of glutamic acid during hypoxia and exercise prevents the accumulation of lactate and pyruvic acid in the blood and maintains the glycogen content in the liver and muscles at higher level [32]. The antioxidant activity of glutamic acid is associated not only with its participation in the glutathione metabolism, but also with the intensive conversion of the latter through succinic semialdehyde into β-hydroxybutyric acid, that lowers cholesterol levels, and corrects acid-base balance.

Glutamic acid produces actoprotective, anabolic and cardioprotective effects. The cardioprotective action is manifested during physical exertion. The most common dosage is 10–15 g (sports dose), or 1 g per day (therapeutic dose). Calcium preparations with glutamic acid are available. Calcium and magnesium glutamate is recommended for the treatment of neuropsychiatric disorders and normalization of peripheral blood parameters [28].

Aspartic acid has a positive effect on indices of collateral coronary circulation and partial pressure of oxygen (pO_2) indicators in myocardial ischemia. The protective effect of aspartate on the body during the action of a closed space is associated with its rapid inclusion in tissue metabolism [15].

Aspartic acid can be included in the malate-aspartate energy shunt and contribute to a significant acceleration in the rate of elimination of ischemic damage indicators in organs and tissues during working hypoxia and a significant increase in the

contractile function of the heart [29]. Aspartic acid enhances the speed of interneuronal interaction and increases the rate of the reaction.

The specificity of the neurotropic action of aspartic acid is explained by the presence in the synaptic endings of enzyme systems for their synthesis and systems that ensure their release into the synaptic cleft under the influence of certain stimuli.

Aspartic acid is involved in the regulation of the endocrine system. Thus, the L-aspartic acid can be converted into the D-aspartic acid, which interacts with certain parts of the hypothalamus and enhances the secretion of gonadotropin-releasing hormone, which indirectly increases testosterone production through the expression of gonadotropin. D-aspartic acid is involved in the release of testosterone and progesterone by the testicles [33]. Aspartic acid is administered at a dose of 3 g/day orally in 2–3 divided doses for 3–5 weeks.

Thiotriazolin (morpholinium 3-methyl-1,2,4-triazolyl-5-thioacetate; thioazotate). The drug exhibits antioxidant, anti-ischemic, and cardioprotective effects. Under conditions of acute working hypoxia, the use of thiotriazoline makes it possible to reduce the formation of lactate due to its utilization and formation of pyruvic acid, as well as activation of the malate-aspartate shunt in mitochondria [34]. Thiotriazoline normalizes the Krebs cycle, enhances ATP production in the myocardium and liver during exercise.

Thiotriazoline exhibits the properties of reactive oxygen species scavenger, inhibits lipid peroxidation reactions, stabilizes cell membranes, and enhances the activity of superoxide dismutase and glutathione peroxidase. It is known that thiotriazoline activates the mechanisms of endogenous cyto- and cardioprotection during ischemia and hypoxia, increasing the expression of the 70 kDa heat shock protein (HSP_{70}), which prolongs the action time of hypoxia-induced factor-1α (HIF-1α), and also independently maintains the expression of NAD-MDH-mx activity; thereby maintaining the activity of the malate-aspartate shuttle mechanism for a long time [35,36].

The mechanism of thiotriazoline effect on physical (including sports) performance has been studied since the 1980s. It is known that preliminary (30 min before exercise in the form of swimming or running) intraperitoneal administration of thiotriazoline (50 mg/kg) to rat produces a actoprotective effect, increasing overall and speed physical endurance due to an increase in ATP levels in the myocardium, a decrease in lactate levels, oxidative stress inhibition and improving ECG parameters [37,38]. There are no opportunities for effective use of thiotriazoline in the practice of sports medicine at the research level. It is known that a single oral intake of thiotriazoline by cyclists-racers at a dose of 200 mg 3 hours before training contributes to a greater use of carbohydrate reserves in working muscles, increases the indicators of maximum oxygen consumption, improves aerobic efficiency, and decreases blood lactate and malondialdehyde levels [35].

L-arginine is the main source of the molecular messenger nitric oxide (NO), which is synthesized under the influence of three forms of NO synthase (NOS): two constitutional – endothelial (eNOS) and neuronal (nNOS), and one inducible (iNOS). The vasodilating effect of L-arginine mediated by NO contributes to the maintenance of vascular tone, normalization of blood pressure, cardio- and systemic hemodynamics [36].

L-arginine has endothelial protective, antioxidant, cardioprotective, hepatoprotective, neuroprotective effects due to the production of NO [28]. Arginine produces an antioxidant effect due to participation in the transamination cycle and excretion of nitrogen waste products, including ammonia, urea and uric acid, which are the breakdown products of protein metabolism, from the body. The ability to synthesize urea and remove protein waste depends on the power of the cycle ornithine – citrulline – arginine. However, NO formed from L-arginine under conditions of liver pathology is rapidly destroyed by free radicals reducing the clinical efficacy of L-arginine [14].

The search for ways to enhance the protective properties of L-arginine by combining it with substances that can improve the energy supply of ischemic myocardium and increase the bioavailability of NO formed from L-arginine is of indisputable interest. These substances include thiotriazoline, which can enhance the cardio- and hepatoprotective effects of L-arginine during physical exertion [28].

The combined action of L-arginine and thiotriazoline, aimed at the synthesis, stabilization and increase in the bioavailability of NO [32,35,36], can be used in the correction of disorders, caused by NO deficiency (physical and mental fatigue, erectile dysfunction, decrease in the reaction rate, etc.).

L-arginine plays an important role in protein synthesis, increasing muscle mass, improving muscle recovery after training, accelerating injury healing and waste removal, optimizing the functioning of the immune system, and increasing the production of growth hormone [29]. Recommended doses of arginine for gaining muscle mass range from 3 g to 9 g per day. The higher the dose, the more noticeable the effect, but exceeding a dose of 10 g is not recommended. Taking the medication is started with the lowest dose and then it is gradually increased. Powder forms are dissolved in water (1 glass), tablets are taken with a glass of water.

Gamma-aminobutyric acid (GABA) is the main inhibitory mediator in the nervous system producing anxiolytic, sedative, anticonvulsant, hypnotic, anti-ischemic, nootropic and vasodilator effects. GABA enhances blood circulation in the cerebral vessels that is accompanied by a decrease in the tone of arteries and arterioles, and practically does not affect venous tone, because GABA receptors are located in the cerebral vessels, in contrast to extracranial vessels [39].

Exogenous introduction of GABA improves the functional state of neurons, although it is known that only a 2 % GABA solution can penetrate the brain tissue. GABA increases ATP levels by being incorporated into a compensatory GABA shunt. As a therapeutic agent, GABA is used under the name aminalon. In addition, GABA is included in the structure of some medications such as picamilon, phenibut (noofen), pantogam [40]. The dosage of GABA is at least 2 g/day. The optimal dose is 3.75 g per day (after training). Small doses of GABA are useless, as only a small portion enters the brain through the blood-brain barrier.

GABA intake is best combined with vitamin B_6, which is a limiting cofactor in the synthesis of neurotransmitters such as dopamine, serotonin, GABA, norepinephrine, and the hormone melatonin. A moderate deficiency of vitamin B_6 can cause inhibition of neuronal GABA activity, various sleep and behavioral

disorders, increased cardiovascular risk, and a decrease in hypothalamic-pituitary hormonal secretion [8,40].

D-gluconic acid is a substrate of the pentose phosphate pathway of glucose oxidation and, after phosphorylation, turns into a phosphoric ester of gluconic acid, which is an important product of cell vital activity [41]. D-gluconic acid regulates the restoring synthesis of plastic processes and energy metabolism, has antihypoxic and antitoxic properties, enhances the properties of antioxidants, including glutathione [29]. It has immunomodulating, wound healing and regenerating activity.

The pharmacological agent **Membraton** is a representative of this class of therapeutic and prophylactic agents, the active ingredients of which are GABA and magnesium compounds of gluconic acid. Doses: 600-1000 mg per day.

Glycine, a CNS inhibitory transmitter, regulates NMDA receptor-mediated neurotransmission in the brain. Glycine produces neuroprotective, anxiolytic, hypnotic, and anti-ischemic effects [42]. Glycine can regulate cerebral circulation due to its effect on a_1-adrenergic receptors. Glycine enhances biotransformation and excretion of products of proteins oxidative modification and other toxic products from the body during oxidative stress caused by ischemia, hypoxia, and exercise. Glycine regulates the synthesis of creatine, which is involved in muscle contraction during intense exercise and frequent training. Glycine improves well-being, boosts physical and mental energy, motivation, relieves tension and mental stress, and normalizes sleep during intense training process. Doses: 100–300 mg per day for 2–5 weeks.

N-acetylcysteine, a derivative of the amino acid cysteine, has mucolytic, detoxifying, antioxidant, and anti-inflammatory effects, utilizes reactive oxygen and nitrogen species, inhibits the initiation of oxidative and nitrosative stress. It also promotes the synthesis of glutathione, an important component of the antioxidant system and chemical detoxification of the body. It inhibits the expression of iNOS and has an anti-inflammatory effect [2,37]. N-acetylcysteine increases resistance to muscle fatigue, which allows increasing the duration of one training session during high- and low-intensity competition preparation. The daily dose is 300–600 mg.

Methionine has a lipotropic effect, promoting the synthesis of choline, the deficiency of which is associated with impaired synthesis of phosphatidylcholine; participates in the production of adrenaline and creatine; activates hormones, vitamins B_{12}, C, and B_6; increases the detoxification potential of the liver: it is used for toxic injury and liver diseases, chronic alcoholism, diabetes, and radiation pathology. Giving a methyl group, methionine stimulates the mobilization of fat from the liver and its oxidation (destruction), which leads to a decrease in the total percentage of fat in the body. Methionine reduces blood cholesterol and normalizes the balance of phospholipids/cholesterol. It has immunomodulating properties, increases body tone and promotes faster recovery after physical exertion [43]. It produces immunostimulating, antioxidant and hepatoprotective activity during physical exertion [44]. The daily dose is 1000 mg per day during active sports. Daily dosages up to 1250 mg per day are acceptable.

Tryptophan is involved in the formation of two biologically active substances that the body needs for normal functioning. Firstly, vitamin B_3 (Niacin), which is formed from tryptophan in the liver, regulates the metabolism of fats and carbohydrates, plays an important role in the metabolism of amino acids, and takes part in redox reactions [45]. Secondly, tryptophan is a precursor of serotonin, a compound involved in many physiological processes. Serotonin acts as a neurotransmitter, affects the secretion of a number of hormones, regulates vascular tone and permeability, affects cellular immunity and controls bowel function. Most of serotonin reserves are located in the mucous membrane of the gastrointestinal tract. Tryptophan may help improve mood, normalize appetite and sleep after maximum physical exertion. Tryptophan is used at all training stages to accelerate recovery after strength training, get rid of excess fat and effectively gain muscle mass [29]. The daily dose is 600–800 mg.

Carnosine, a dipeptide beta-alanyl-histidine made up of the amino acids: beta-alanine and histidine. It is highly concentrated in muscles, heart, and brain tissues. It exhibits the properties of an active antioxidant, regulates the expression of antioxidant enzymes, and has cardioprotective and neuroprotective properties [46]. Carnosine increases myocardial contractile activity, limits the intensity of oxidative stress, anaerobic glycolysis and glycogenolysis in the myocardium under conditions of working hypoxia [47]; it exhibits a wound healing effect, accelerates reparative processes by activating fibroblast proliferation [48]. Carnosine has antiaging, retinoprotective, and immunomodulating properties [33]. The main area of use of L-carnosine is professional sports. For heavyweight athletes and bodybuilders, the substance is valuable because it provides the following biological effects: increased endurance during anaerobic loads, increased overall working power of training, and reduced rest time [49]. Carnosine is used to increase endurance during physical exertion; it is also effective in inflammatory processes; and as a wound healing and stress-protective agent [49]. The common dosage is 500 mg (1 capsule) daily with meals, and if necessary – 1000–1500 mg (2–3 capsules). Course 1–2 months. The course can be repeated 2–3 times a year.

L-carnosine provides muscle protection during increased physical exertion and helps to increase their performance; enhances contractions of tired muscles with further prolonged muscle work [22]. L-carnosine also accelerates wound healing, promotes the fusion of bone fragments after injuries [50]. Under the influence of the drug, the physical capabilities of a person increase, especially in extreme situations. L-carnosine also normalizes the function of the central nervous system and exhibits neuroprotective properties. The drug is included in the complex therapy of traumatic brain injuries, and is administered to increase concentration, improve memory, and complex thought processes. The course of treatment is 8–10 weeks. The recommended daily dose is 500 mg 1 hour before meals with a glass of clean water. If necessary, the dose may be increased to 1000 mg. Sometimes the daily dosage is 2500 mg. It all depends on the specific situation.

Nicotinamide is a catalytically active group of nicotinamide coenzymes, which plays an important role in almost all energy-dependent processes and exhibits antihypoxic, cytoprotective, and anti-ischemic effects [34]. Nicotinamide is a prostatic group of the nicotinamide coenzymes codehydrase I (diphosphopyri-

dine nucleotide, nicotinamide adenine dinucleotide, NAD) and codehydrase II (3-phosphopyridine nucleotide, NADP), which carry hydrogen and carry out redox processes associated with energy production. Nicotinamide in small doses increases glucose utilization and activates glycogenase, but at high dose levels, this effect of nicotinamide is not realized.

Nicotinamide may increase appetite and promote weight gain due to two-phase fluctuations in blood glucose and insulin levels. Despite this, the drug can be found in fat burners and pre-workout nutritional supplements. Nicotinamide normalizes insulin and glucagon levels during working hypoxia; at high dose levels, it inhibits lipolysis in adipose tissue, reduces the levels of atherogenic lipoproteins in the blood; and may reduce the atherogenic effect of steroid drugs. Nicotinamide increases the rate of mitochondrial oxidation and phosphorylation processes and leads to an increase in ATP levels in the muscles. Nicotinamide can potentiate the energotropic action of L-carnitine by regulating mitochondrial palmitic pore activity.

Nicotinamide, together with GABA, significantly increases the rate of cerebral blood flow, which leads to an improvement in the cognitive-memory functions of the CNS. Due to its positive effect on energy metabolism and mitoprotective activity, nicotinamide can be useful in bodybuilding and other sports as a substance that increases the performance of the training process [29]. Doses: 20–500 mg per day.

Succinic acid (succinate) is the most important participant in the tricarboxylic acid cycle, or the Krebs cycle. External addition of succinate activates the Krebs cycle. Succinic acid exhibits antihypoxic, anti-ischemic, cytoprotective, adaptogenic, actoprotective and antioxidant effects. Succinic acid provides efficient transport of electrons and protons into mitochondria and increases the reduction of ubiquinone [16]. The antihypoxic and anti-ischemic effects of succinic acid may be associated with the activation of succinate dehydrogenase oxidation and the restoration of the cytochrome oxidase, the key enzyme of the mitochondrial redox chain redox chain.

A combination of **sodium succinate** and **cytochrome C** is promising from the point of view of energy-tropic and anti-ischemic action. Sodium salts of succinate are effective in reducing metabolic acidosis due to intracellular oxidation with the replacement of one hydrogen molecule by sodium with the formation of bicarbonate [8,19].

The antioxidant effect of succinates is realized due to the inhibition of the production of reactive oxygen species by energy-producing reactions of mitochondria (Castell et al., 2015). The antioxidant effect of succinate is manifested in the reduction of oxidative stress products, in particular carbonylated proteins. Succinic acid activates the synthesis of the endogenous antioxidant glutathione [51].

Succinates stimulate erythropoiesis. When using low doses about 50 mg/day, the activation of synthesis and action of adrenaline, norepinephrine and dopamine can be the leading mechanism. Due to this, succinate also has a psychostimulating, normothymic and antidepressant action, which is most pronounced in ammonium succinate. At the same time, ammonium succinate causes an acceleration of recovery after intense exercise. Succinic acid exhibits detoxifying and anti-hangover properties, accelerating the biotransformation of acetaldehyde [52]. In sports medicine, succinic acid is used for extreme physical and psycho-emotional training and competitive loads, during the recovery period of the training process, if necessary, to produce an anti-ischemic and anti-hypoxic effects. Constant courses that gently support regulatory mechanisms should be based on doses of 50-100 mg per day; at the same time, intermittent courses (a few days of admission, a few days of rest, e. g., modes 5–2, 7–3) shroud be used. Sometimes the dose of succinic acid should be increased to 1–2 g. Succinic acid is administered with caution in diseases of the digestive system.

Malate is a dicarboxylic acid that provides the body with the necessary energy. During the synthesis of dicarboxylic acid, oxidative phosphorylation and ATP breakdown occur; and free energy necessary to maintain metabolic processes begins to be released. Malate has a stimulating effect on the Krebs cycle [53], that reduces the content of lactate in tissues and blood and increases energy production in cells. In addition, ATP level increases and lactic acidosis does not develop. Malate provides power to the compensatory cytosolic-mitochondrial shunt mechanism, the malate-aspartate shunt. The malate-aspartate shunt mechanism carries out the transfer of reduced equivalents formed in the cytoplasm during glycolysis to mitochondria under conditions of ischemia [8].

$NADH^+$ formed in cytoplasm under conditions of low oxygen content is used to convert oxaloacetic acid to malate, which penetrates the mitochondria and participates in the transport of α-ketoglutarate [54]; in mitochondria it turns into oxaloacetic acid with the formation of NADH, available for the electron transport chain (3 ATP molecules are formed from 2 protons). Oxaloacetic acid formed from malate is converted into α-ketoglutarate and aspartate. Alpha-ketoglutarate comes from the mitochondria in exchange for malate, and aspartate is exchanged for glutamate; transport occurs due to the glutamate gradient and the high intramitochondrial glutamate-aspartate ratio. The malate-aspartate shunt provides ATP to organs and tissues under conditions of ischemia and significant physical exertion [55].

Malate-aspartate shunt is active in the heart, muscles, and brain. Due to this, malate produces antihypoxic, anti-ischemic, cardioprotective and actoprotective effects. Malate is administered for asthenic syndrome, emotional exhaustion, diabetic asthenia, asthenic syndrome in athletes due to prolonged physical exertion; severe fatigue, overwork; muscle cramps; sexual asthenia; alcohol withdrawal syndrome; pain after exercise; after heavy physical exertion, which causes overload of the body [56]; to alleviate myalgia in athletes after intense training and to correct acidosis [22]. Malate is available as Magnesium malate, Calcium malate, and Citrulline malate. The common dosage is 400–800 mg 2–3 times a day.

Citrate, a salt or ester of citric acid, creates ergogenic potential by increasing the pH gradient between blood and muscles and interacting with hydrogen ions. Citrate penetrates muscle fibers and can influence glycolysis reactions [57]. In alpine skiing, before difficult and long training tasks (two-minute descent at maximum intensity), sodium citrate should be taken to reduce the degree of muscle acidification [55]. There is evidence that citrate does not affect the amount of work performed and can lead to alkalosis.

Rehydron, a complex preparation of electrolytes with carbohydrates for oral rehydration, contains potassium chloride 2.5 g; sodium chloride 3.5 g; sodium citrate 2.9 g; and anhydrous glucose 10 g. Rehydron is administered to restore water and electrolyte balance, correct acidosis in acute diarrhea, mild and moderate dehydration (for example, loss of 3–9 % of body weight in children), with thermal injuries accompanied by impaired water and electrolyte metabolism. With a preventive purpose, rehydron is used for thermal and physical exertion, leading to intense sweating. Content of 1 sachet of Rehydron is dissolved in 1 L newly boiled water, cooled at room temperature, taken orally, or administered through a nasogastric tube.

Pyruvate is a key metabolite of carbohydrate metabolism and is involved in the Krebs cycle, a process in which cells produce energy in the form of ATP through acetylation with acetyl coenzyme A (acetyl-CoA). As the body's main chemical fuel, ATP drives key vital body functions, including muscle movement.

Pyruvate is also important in other metabolic processes, including fat and protein metabolism, glycogen storage, and promotes the activation of lipolytic enzymes. Therefore, pyruvate quickly replenishes the supply of cellular fuel and contributes to energy production. Pyruvate is an intermediate in gluconeogenesis and glycogen storage. Pyruvate can be converted to alanine, an amino acid that is a source of glucose.

Calcium pyruvate is a supplement that was first introduced in the late 1990s, based on data that its administration at a dose of 16–25 g per day, together with dihydroacetone phosphate, contributed to weight loss in patients undergoing treatment for obesity. The mechanism of action of calcium pyruvate may be based on appetite suppression and/or influence on carbohydrate and fat metabolism. Calcium pyruvate is an extremely expensive supplement, so some researchers have been trying to figure out if smaller doses (6–16 g per day) can affect changes in body structure. Pyruvate salts are widely used by bodybuilders, cyclists, runners, and soccer players [22].

It has been established that pyruvate, together with L-carnitine, increase endurance during aerobic exercise by enhancing lipolysis by shifting the energy preferences of mitochondria towards fatty acids and increasing ATP production [55]. Pyruvate also increases skeletal muscle glucose transport. As an energotropic agent, pyruvate has found use in those sports that require significant endurance including running and swimming. It has been experimentally found that pyruvate has antioxidant and anti-aging properties [58]. Pyruvate is available in 1000 mg tablets, and solution of potassium pyruvate with vitamin C is available in ampoules. Sometimes pyruvate is included in the composition of megapackets and protein complexes but the concentration of pyruvate there is insufficient for a daily therapeutic dose.

Beta-alanine, a naturally occurring amino acid, is a component of many proteins, connective tissue, it is also a part of vitamin B_5 (pantothenic acid). In the human body, beta-alanine is synthesized from carnosine. Alanine can also be converted from leucine, isoleucine and valine. In sports, beta-alanine is positioned as an ergogenic drug (along with creatine and arginine) increasing overall efficiency. Alanine can also be synthesized from branched chain amino acids such as leucine, isoleucine, and valine.

Beta-alanine supplementation is mainly administered to increase muscle endurance, improve exercise capacity, particularly when performing short bursts of high-intensity exercise. Beta-alanine effectively eliminates muscle pain after training and speeds up recovery from injuries. Beta-alanine is necessary for athletes facing anaerobic stress, including bodybuilders, as it helps to increase the intensity of training, and hence the growth of muscles. Studies have shown that beta-alanine is of no value to track and field athletes. It does not affect blood hormone levels (testosterone, cortisol) in exercising athletes [59]. It was shown that a 4-week course of taking beta-alanine had no effect on mental activity, but increased static endurance, aiming speed, and shooting accuracy. There is evidence of some positive changes and the effectiveness of the practical use of beta-alanine and various aspects of its action over the past 10 years [29] including the following:

– beta-alanine exerts its activity by increasing the concentration of carnosine in the muscles, acting as an intracellular pH buffer. A decrease in lactate content and pH correction accelerates the recovery process after exercise. To increase carnosine levels in the body, a course intake of beta-alanine at a dose of 4–6 g per day (about 4 weeks) is required;

– beta-alanine increases the efficiency of performing high-intensity physical exercises lasting more than 60 sec, and the duration of training to failure (to exhaustion);

– during physical exertion that requires a very high proportion of the aerobic pathway of energy production, beta-alanine improves the recorded performance indicators in the process of the load testing;

– beta-alanine can produce an antioxidant effect;

– taking beta-alanine supplements at doses of 4–6 g per day for 2–4 weeks improves physical fitness, with the most pronounced effect when performing tasks lasting from one to four minutes;

– beta-alanine reduces neuromuscular fatigue, especially in older people;

– when solving tactical problems performing physical exertion, beta-alanine contributes to their more successful implementation.

– the combined use of beta-alanine with other single or complex nutritional supplements may have certain advantages, subject to the sufficiency of its dose and course appointment;

– the daily dose of alanine for people involved in bodybuilding, fitness, weightlifting is 3–6 g per day (1–2 g thrice a day). The course is 8–12 weeks. People who do not lead an active lifestyle are recommended up to 1 g per day.

Many studies have shown that taking even high doses of beta-alanine is not capable of causing any health problems.

After the combined administration of beta-alanine with sodium bicarbonate or creatine, there is a moderate increase in the ergogenic effect compared with the separate use of these substances. The combination of these components in one dietary supplement to increase physical fitness can be effective if the duration of use is sufficient to increase the level of carnosine in the muscles, and the complex product is used for at least 4 weeks.

Despite some limited evidence to date, there is a consolidated view of the safety of beta-alanine when used in healthy individuals at recommended doses. Side effects (paresthesia) do not affect the result of the application, are transient and significantly reduced during course use.

Cytochrome-C has significant antihypoxic activity and anti-ischemic effect [60]. It has been shown that cytochrome-C during hypoxia contributes to the normalization of energy-producing oxidative phosphorylation, increases the endurance and performance of the body. In bodybuilding cytochrome-C is used as a special purpose food supplement that increases the rate of chemical reactions in cells.

Cytochrome-C is recommended to be taken a week before the start of the competition. Bodybuilding with increased loads has a stressful effect, and the agent, which affects the processes of tissue respiration, enhances oxidative reactions, and helps to endure physical activity without consequences for the body. Cytochrome-C is recommended for use by beginner athletes working to improve their endurance levels. It is especially effective for recovery strategies in athletes with elevated blood lactate levels [2]. In bodybuilding, the common dosage for cytochrome-C is 15–20 mg orally 4 times a day for 50 days. Parenterally, cytochrome-C is used at the end of a workout for accelerated recovery and rest of athletes, since after an increased load, the body does not have time to recover on its own before the start of the next load. In this case, 15 mg of cytochrome-C is administered intramuscularly for 10 days.

Quercetin is one of the most powerful antioxidants not only among flavonoids, but also among compounds of other groups. Quercetin is superior to alpha-tocopherol and retinol in its antioxidant properties. In the most general terms, the bioflavonoid quercetin can be characterized as a powerful antioxidant, an inhibitor of leukotriene synthesis, a complex signal conduction and realization blocker in the calcium-mobilizing phosphatidylinositol cycle, and an activator of the adenylate cyclase signaling cascade.

These mechanisms determine most of the pharmacotherapeutic effects of quercetin. It has been established that the antihypoxic effect of quercetin is directly related to its antioxidant properties [28]. It has been shown that quercetin prevents the disturbance of the body's oxidative homeostasis, which underlies the pathogenesis of hypoxic syndrome. The protective effect of quercetin has been established under the combined action of hypoxia and hyperthermia on the body [34].

Quercetin has a vasodilator property due to several mechanisms of action. At the level of vascular smooth muscle cells, quercetin prevents vasoconstriction by disrupting calcium entry into the cell. This is due to the blockade of the processes of protein kinase phosphorylation and, ultimately, the function of calcium ATPase. Acting at the level of the endothelium, quercetin inactivates the enzyme adenosine deaminase. This increases the content of endogenous adenosine in endothelial cells and leads to vasodilation. In addition, quercetin enhances endothelial production of nitric oxide, a potent vasorelaxant mediator. Possible mechanisms of the antiplatelet action of quercetin include inhibition of leukotriene synthesis, inhibition of Ca^{2+} influx into platelets, and blockade of phospholipase D [29]. The anticoagulant effect of quercetin, which manifests in the inhibition of the catalytic activity of thrombin in the fibrinogen binding reaction, may be important.

Due to its antioxidant properties, quercetin and its complexes are used in sports. Quercetin is often used in bodybuilding and included in sports nutrition. The studies showed that quercetin increased energy expenditure in mice and improved exercise tolerance. This may indicate that quercetin can be used in fat-burning complexes, as well as to increase physical performance. Quercetin is recommended to be combined with vitamin C, since these substances potentiate the positive effects of each other; and with bromelain, which increases quercetin absorption [2].

Beta-hydroxy-beta-methylbutyrate (HMB) is a relatively new nutritional supplement that is gaining interest in sports medicine. HMB-FA (acid form of HMB) and HMB-Ca (calcium salt of HMB) are structural analogues of butyric acid and butyrate, which have a hydroxy and a methyl groups at the β-carbon atom.

The mechanism of action of HMB is closely related to the metabolism of leucine. It is known that oral administration of a course of the branched-chain amino acid (BCAA) leucine during constant training can increase strength and lean body mass (LBM) while reducing fat body mass (FBM). Leucine reduces soreness of skeletal muscles during ultra-intense exercise, prevents a decrease in circulating testosterone and the decrease in of skeletal muscle force after ultra-high exercise, and provides additional adaptation to strength training due to the activation of skeletal muscle signaling pathways related to protein synthesis [18]. It has been established that the effects are mediated by specific leucine metabolites, one of which is HMB [29]. There is a lot of evidence of a diverse positive influence (ergogenic effect) of HMB in sports such as acceleration of recovery after physical exertion, an increase in skeletal muscle force, body weight; a decrease in body fat, and an increase- in physical strength when performing aerobic and anaerobic movements [7]. The position in relation to the HMB boils down to the following:

– HMB can be used to improve recovery processes by reducing muscle damage during training in both trained and untrained individuals;

– the effectiveness of oral intake of HMB is manifested exclusively in direct connection with the training cycle;

– HMB is most effective when used with a course appointment 2 weeks before the end of training;

– a daily dose 38 mg/kg is considered effective in increasing muscular strength and power, and skeletal muscle hypertrophy in both trained and untrained individuals, provided an adequate training program is followed. This means that the total daily dose of HMB is about 3 g divided into 2 doses;

– oral intake of HMB combined with structured training programs can significantly reduce FBM;

– the mechanism of action of HMB during exercise includes suppression of proteolysis and activation of protein synthesis;

– chronic (permanent) use of HMB is safe both in young and older adults.

The effective use of HMB (3 g per day) requires 2 or more weeks, shorter periods are ineffective. Thus, the intake of Ca-HMB is optimal if it is used 2 weeks before the start of a new training cycle, and 60 min before physical activity.

Discussion

It is known that from 40 % to 88 % of athletes take metabolitotropic and metabolite agents and nutritional supplements for special purposes. Aggressive marketing has spurred millions

of amateur and elite athletes to use these products in hopes of improving athletic performance. In the USA alone, more than 3 million people use them on their own.

However, to date there is no evidence base for efficacy and safety for most of these supplementary agents. The most studied among them are metabolitotropic agents that improve energy metabolism and are either macroergic compounds, substrates, intermediates of energy metabolism, or pharmacological modulators of subtle links of energy metabolism [2,6,10,19,33,60].

All discussed pharmacological agents perform a task on increasing the physical performance in athletes, accelerating the processes of their body adaptation to high-intensity physical activity by replenishing ATP reserves. There are convincing data on the effectiveness of metabolite drugs based on succinate, malate, pyruvate, GABA, creatine phosphate and ATP; and metabolite agents such as L-carnitine, riboxin, and thiotriazoline.

Additional experimental and clinical studies of efficacy and safety require pharmacological agents and nutritional supplements based on amino acids, HMB, etc. Sports physicians working with athletes should have accurate information about metabolite and metabolitotropic drugs, and nutritional supplements; know their mechanisms of action, desired effects in sport and side effects, and whether the supplement is prohibited by leagues or organizations in which athletes compete. Also, sports coaches, strength and conditioning coaches, and sports nutritionists, who are important sources of information for athletes about the pharmacological properties of these agents, should receive knowledge not from the Internet or from sales representatives (which is the reason for inconsistency regarding medical recommendations), but from scientific and methodological manuals and articles. All this will provide a scientific basis for the rational use of metabolites, metabolitotropic agents and nutritional supplements that can affect the main and compensatory mechanisms of macroergic phosphates production under the influence of physical activity.

Conclusions

Thus, based on the semantic analysis of data currently available, the necessary task of sports doctors and pharmacologists is the development of metabolitotropic agents and nutritional supplements, and approaches to their rational combination in order to improve energy metabolism and replenish ATP reserves in the body to ensure the high intensity of muscle contractions and at the same time protect target organs.

Acknowledgment
The authors would like to acknowledge the Zaporizhzhia State Medical and Pharmaceutical University for providing some facilities in carrying out the research.

Information about the authors:
Bielenichev I. F., PhD, DSc, Professor, Head of the Department of Pharmacology and Medical Formulation with Course of Normal Physiology, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0003-1273-5314
Gorchakova N. O., MD, PhD, DSc, Professor of the Department of Pharmacology, Bogomolets National Medical University, Kyiv, Ukraine.
ORCID ID: 0000-0002-7240-5862
Doroshenko E. Yu., PhD, DSc, Professor, Head of the Department of Physical Rehabilitation, Sports Medicine, Physical Education and Health, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0001-7624-531X
Samura I. B., MD, PhD, Associate Professor of the Department of Pharmacology and Medical Formulation with Course of Normal Physiology, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0001-5352-3209
Ryzhenko V. P., MD, PhD, Associate Professor of the Department of Medical and Pharmaceutical Informatics and Advanced Technologies, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0003-3466-7148
Bukhtiiarova N. V., MD, PhD, Associate Professor of the Department of Clinical Laboratory Diagnostic, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0003-3499-3111

Відомості про авторів:
Бєленічев І. Ф., д-р біол. наук, професор, зав. каф. фармакології та медичної рецептури з курсом нормальної фізіології, Запорізький державний медико-фармацевтичний університет, Україна.
Горчакова Н. О., д-р мед. наук, професор каф. фармакології, Національний медичний університет імені О. О. Богомольця, м. Київ, Україна.
Дорошенко Е. Ю., д-р наук з фіз. виховання та спорту, професор, зав. каф. фізичної реабілітації, спортивної медицини, фізичного виховання та здоров'я, Запорізький державний медико-фармацевтичний університет, Україна.
Самура І. Б., канд. мед. наук, доцент каф. фармакології та медичної рецептури з курсом нормальної фізіології, Запорізький державний медико-фармацевтичний університет, Україна.
Риженко В. П., канд. мед. наук, доцент каф. медичної та фармацевтичної інформатики і новітніх технологій, Запорізький державний медико-фармацевтичний університет, Україна.
Бухтіярова Н. В., канд. мед. наук, доцент каф. клінічної лабораторної діагностики Запорізький державний медико-фармацевтичний університет, Україна.

References

1. Orchard JJ, Maddocks D, Carneiro E, Orchard JW. A review of legal, ethical, and governance issues for team doctors. Clin J Sport Med. 2022;32(3):248-55. doi: 10.1097/JSM.0000000000000986
2. Gunina LM, Shustov YB, Belenichev IF, Vysochina NL, Golovashchenko RV, Morozova OV. Specialized nutrition for athletes: evaluation of ergogenic action using the principles of evidence-based medicine. Pharmacia. 2022;69(1):37-44. doi: 10.3897/pharmacia.69.e76599
3. Abbey EL, Wright CJ, Kirkpatrick CM. Nutrition practices and knowledge among NCAA Division III football players. J Int Soc Sports Nutr. 2017;14:13-22. doi: 10.1186/s12970-017-0170-2
4. Baltazar-Martins G, de Souza DB, Aguilar-Navarro M, Muñoz-Guerra J, Plata MD, Del Coso J. Prevalence and patterns of dietary supplement use in elite Spanish athletes. J Int Soc Sports Nutr. 2019;16(1):e30. doi: 10.1186/S12970-019-0296-5
5. Greg A, Alan MN. Statistical methods for assessing measurement error (reliability) in variables relevant to sports medicine. Sports Med. 1998;26(4):217-38. doi: 10.2165/00007256-199826040-00002
6. Otten JJ, Hellwig JP, Meyers LD, editors. Dietary reference intakes: The essential guide to nutrient requirements. Washington, DC: The National Academies Press. 2006 [cited 2023, Jun 28]. Available from: http://nap.edu/openbook.php?record_id=11537
7. Thomas DT, Erdman KA, Burke LM. Position of the Academy of Nutrition and Dietetics, Dietitians of Canada, and the American College of Sports Medi-

cine: Nutrition and Athletic Performance. J Acad Nutr Diet. 2016;116(3):501-28. doi: 10.1159/000345862
8. Belenichev IF, Chernii VI, Kolesnik YM, Pavlov SV. [Rational neuroprotection]. Donetsk: ID Zaslavskii; 2009. Russian.
9. Close GL, Hamilton DL, Philp A, Burke LM, Morton JP. New strategies in sport nutrition to increase exercise performance. Free Radic Biol Med. 2016;98:144-58. doi: 10.1016/j.freeradbiomed.2016.01.016
10. Belenichev I, Gorchakova N, Kuchkovskyi O, Ryzhenko V, Varavka I, Varvanskyi P, et al. Principles of metabolithotropic therapy in pediatric practice. Clinical and pharmacological characteristics of modern metabolithotropic agents (part 1). Phytotherapy. Journal. 2022;3:6-26. doi: 10.33617/2522-9680-2022-3-6
11. Ahmad NS, Abdul Aziz A, Kong, KW, Hamid MSA, Cheong JPG, Hamzah SH. Dose-response effect of tualang honey on postprandial antioxidant activity and oxidative stress in female athletes: A pilot study. J Altern Complement Med. 2017;23(12):989-95. doi: 10.1089/acm.2017.0129
12. Mazur I, Belenichev I, Kucherenko L, Bukhtiyarova N, Puzyrenko A, Khromylova O, et al. Antihypertensive and cardioprotective effects of new compound 1-(β-phenylethyl)-4-amino-1,2,4-triazolium bromide (Hypertril). Eur J Pharmacol. 2019;853:336-44. doi: 10.1016/j.ejphar.2019.04.013
13. Belenichev IF, Cherniy VI, Nagornaya EA, Bukhtiyarova NV, Kucherenko VI. [Neuroprotection and Neuroplasticity]. Kiev: Logos; 2015. Russian.
14. Abel T, Knechtle B, Perret C, Eser P, von Arx P, Knecht H. Influence of chronic supplementation of arginine aspartate in endurance athletes on performance and substrate metabolism – a randomized, double-blind, placebo-controlled study. Int J Sports Med. 2005;26(5):344-9. doi: 10.1055/s-2004-821111
15. An D, Zeng Q, Zhang P, Ma Z, Zhang H, Liu Z, et al. Alpha-ketoglutarate ameliorates pressure overload-induced chronic cardiac dysfunction in mice. Redox Biol. 2021;46:102088. doi: 10.1016/j.redox.2021.102088
16. Xu G, Yuan Y, Luo P, Yang J, Zhou J, Zhu C, et al. Acute succinate administration increases oxidative phosphorylation and skeletal muscle explosive strength via SUCNR1. Front Vet. Sci. 2022;8:808863. doi: 10.3389/fvets.2021.808863
17. Burke LM. Practical issues in evidence-based use of performance supplements: supplement interactions, repeated use and individual responses. Sports Med. 2017;47(Suppl. 1):79-100. doi: 10.1007/s40279-017-0687-1
18. Hunter GR, Fisherm G, Neumeier WH, Carter SJ, Plaisance EP. Exercise training and energy expenditure following weight loss. Med Sci Sports Exercise. 2015;9:1950-7. doi: 10.1249/MSS.0000000000000622
19. Hunina LM, Ataman YO, Belenichev IF, Voitenko VL, Nosach OV. Laboratornyi monitoring i netrytyvno-metabolichna pidtrymka protsesu pidhotovky sportsmeniv [Laboratory monitoring and nutritional and metabolic support of the training process of athletes]. Sumy: SumDU; 2023. Ukrainian. https://essuir.sumdu.edu.ua/bitstream-download/123456789/91724/3/Hunina_nutrytyvno_metabolichna_pidtrymka.pdf
20. Belenichev IF, Aliyeva OG, Bukhtiyarova NV, Popazova OO, Ryzhenko VP. Positive Pharmacological Modulation of Hsp70 in Recovery of Brain Energy Metabolism in Various Models of Cerebral Ischemia. Biol Life Sci Forum. 2022;20(1):24. doi: 10.3390/IECBM2022-13511
21. Anders JPV, Neltner TJ, Smith RW, Keller JL, Housh TJ, Daugherty FJ, et al. The effects of phosphocreatine disodium salts plus blueberry extract supplementation on muscular strength, power, and endurance. J Int Soc Sports Nutr. 2021;18(1):60. doi: 10.1186/s12970-021-00456-y
22. Wu Y, Liu H, Wang X. Cardioprotection of pharmacological postconditioning on myocardial ischemia/reperfusion injury. Life Sci. 2021;264:118628. doi: 10.1016/j.lfs.2020.118628
23. Blomstrand E, Mooren FC, Krüger K, Kavazis AN, Quindry JC, Senchina DS, et al. Consensus statement immunonutrition and exercise. Exerc Immunol Rev. 2017;23:8-50.
24. Shu J, Shi J, Gu Y, Deng L, Zhao C, Wu C, et al. Levocarnitine regulates the growth of angiotensin II-induced myocardial fibrosis cells via TIMP-1. Open Life Sci. 2023;18(1):20220554. doi: 10.1515/biol-2022-0554
25. Emran T, Chowdhury NI, Sarker M, Bepari AK, Hossain, M., Rahman GMS, et al. L-carnitine protects cardiac damage by reducing oxidative stress and inflammatory response via inhibition of tumor necrosis factor-alpha and interleukin-1beta against isoproterenol-induced myocardial infarction. Biomed Pharmacother. 2021;143:112139. doi: 10.1016/j.biopha.2021.112139
26. Belenichev IF, Vizir VA, Mamchur VI, Kuriata OV. [Place of tiotriazoline in the gallery of modern metabolitotropic medicines]. Zaporozhye Med J. 2019;21(1):119-28. Russian. doi: 10.14739/2310-1210.2019.1.155856
27. Jin CL, Ye JL, Yang J, Gao CQ, Yan HC, Li H.C, et al. mTORC1 mediates lysine-induced satellite cell activation to promote skeletal muscle growth. Cells. 2019;8(12):1549. doi: 10.3390/cells8121549
28. Belenichev IF, Reznichenko YG, Reznichenko NY, Ryzhenko OI. [Perinatal lesions of the nervous system]. Zaporozhye: Prosvita; 2020. Russian.
29. Castell LM, Stear SJ, Burke LM, editors. Nutritional supplements in sport, exercise and health: An A-Z Guide. London: Routledge; 2015. doi: 10.4324/9781315772509
30. Belenichev IF, Nagornaya EA, Gorbacheva SV, Gorchakova NA, Bukhtiyarova NV. [Thiol-disulfide system: role in endogenous cyto- and organoprotection, pathways of pharmacological modulation]. Kyiv: Euston Publishing House; 2020. Russian.
31. Kurtz JA, VanDusseldorp TA, Doyle JA, Otis JS. Taurine in sports and exercise. J Int Soc Sports Nutr. 2021;18(1):39. doi: 10.1186/S12970-021-00438-0
32. Parkhomenko D, Belenichev I, Bukhtiyarova N, Kuchkovskyi O, Gorchakova N, Diachenko V, et al. Pharmacocorrection of Disturbances in the NO System in Experimental Chronic Generalized Periodontitis. Open Access Maced J Med Sci. 2023;11(A):47-52. doi: 10.3889/oamjms.2023.10717
33. Drake KJ, Sidorov VY, McGuinness OP, Wasserman DH, Wikswo JP. Amino acids as metabolic substrates during cardiac ischemia. Exp Biol Med (Maywood). 2012;237(12):1369-78. doi: 10.1258/ebm.2012.012025
34. Belenichev IF, Chekman IS, Mazur IA, Gorchakova NA, Voloshin NA, Kucherenko LI. [Metabolitotropic drugs]. Zaporozhye: Pechatnyi Dom, 2007. Russian.
35. Belenichev IF, Aliyeva OG, Popazova OO, Bukhtiyarova NV. Involvement of heat shock proteins HSP70 in the mechanisms of endogenous neuroprotection: the prospect of using HSP70 modulators. Front Cell Neurosci. 2023;17:1-16. doi: 10.3389/FNCEL.2023.1131683
36. Maslennikov SO, Golovakha ML, Belenichev IF, Makyeyeva LV. Regenerative properties of polypropylene mesh coated with thiotriazoline and L-arginine. Biomed Pharmacol J. 2022;15(4). doi: 10.13005/BPJ/2537
37. Belenichev I, Gorbachova S, Pavlov S, Bukhtiyarova N, Puzyrenko A, Brek O. Neurochemical status of nitric oxide in the settings of the norm, ischemic event of central nervous system, and pharmacological intervention. Georgian Med News. 2021;315:169-76.
38. Belenichev I, Kucherenko L, Pavlov S, Bukhtiyarova N, Popazova O, Derevianko N, et al. Therapy of post-COVID-19 syndrome: improving the efficiency and safety of basic metabolic drug treatment with tiazotic acid (thiotriazoline). Pharmacia. 2022;69(2):509-16. doi: 10.3897/pharmacia.69.e82596
39. Zacharopoulos G, Sella F, Cohen Kadosh K, Hartwright C, Emir U, Cohen Kadosh R. Predicting learning and achievement using GABA and glutamate concentrations in human development. PLoS Biol. 2021;19(7):e3001325. doi: 10.1371/journal.pbio.3001325
40. Burke LM, Castell LM, Case DJ, Close GC, Costa RJS, Desbrow B, et al. International Association of Athletics Federations Consensus Statement 2019: Nutrition for athletics. Int J Sport Nutr Exerc Metab, 2019;29(2):73-84. doi: org/10.1123/ijsnem.2019-0065
41. Son H, Han SU, Lee K. 2,5-Diketo-D-Gluconate Hyperproducing Gluconobacter sphaericus SJF2-1 with Reporting Multiple Genes Encoding the Membrane-Associated Flavoprotein-Cytochrome c Complexed Dehydrogenases. Microorganisms. 2022;10(11):2130. doi: 10.3390/MICROORGANISMS10112130
42. Maughan RJ, Burke LM, Dvorak J, Larson-Meyer DE, Peeling P, Phillips SM, et al. IOC consensus statement: dietary supplements and the high-performance athlete. British J Sports Medicine. 2018;52(7):439-55. doi: 10.1136/bjsports-2018-099027
43. Chen H, Wang Z., Wang Z, Dou J, Zhou C. Improving methionine and ATP availability by MET6 and SAM2 co-expression combined with sodium citrate feeding enhanced SAM accumulation in Saccharomyces cerevisiae. World J Microbiol Biotechnol, 2016;32(4):56. doi: 10.1007/s11274-016-2010-y
44. Hariharan S, Dharmaraj S. Selenium and selenoproteins: it's role in regulation of inflammation. Inflammopharmacology. 2020;28(3):667-95. doi: 10.1007/s10787-020-00690-x
45. Gonzalez MJ, Miranda-Massari JR. Diet and stress. Psychiatr Clin North Am. 2014;37(4):579-89. doi: 10.1016/j.psc.2014.08.004
46. Renner C, Asperger A, Seyffarth A, Meixensberger J, Gebhardt R, Gaunitz F, Carnosine inhibits ATP production in cells from malignant glioma. Neurol Res. 2010;32(1):101-5. doi: 10.1179/016164109X12518779082237

47. Garthe I., Maughan RJ. Athletes and supplements: Prevalence and perspectives. Int J Sport Nutr Exerc Metab, 2018;28(2):126-38. doi: 10.1123/ijsnem.2017-0429
48. Shen Y, Yang J, Li J, Shi X, Ouyang L, Tian Y, et al. Carnosine inhibits the proliferation of human gastric cancer SGC-7901 cells through both of the mitochondrial respiration and glycolysis pathways. PLoS One, 2014;9(8):e104632. doi: 10.1371/journal.pone.0104632
49. Varanoske AN, Hoffman JR, Church DD, Wang R, Baker KM, Dodd SJ, et al. Influence of skeletal muscle carnosine content on fatigue during repeated resistance exercise in recreationally active women. Nutrients. 2017;9(9):988. doi: 10.3390/nu9090988
50. Kalbe C, Metzger K, Gariépy C, Palin MF. Effect of muscle fibre types and carnosine levels on the expression of carnosine-related genes in pig skeletal muscle. Histochem Cell Biol. 2023;160:63-77. doi: 10.1007/s00418-023-02193-6
51. Gunina LM. [A validity of the use of compositions on the basis of succinic acid in higher achievements sports]. Pedagog psychol med-biol probl phys train sports. 2012;5:50-4. Ukrainian. https://www.sportpedagogy.org.ua/html/journal/2012-05/html-en/12glmhas.html
52. Rosenbloom C. Protein power: answering athletes' questions about protein. Nutr Today. 2015;50(2):72-7. doi: 10.1097/NT.0000000000000083
53. Gleeson M. Immunological aspects of nutrition. Review. Immunol Cell Biol. 2016;94(2):117-23. doi: 10.1038/icb.2015.109
54. Alves PM, Nunes R, Zhang C, Maycock CD, Sonnewald U, Carrondo MJ et al. Metabolism of 3–(13)C–malate in primary cultures of mouse astrocytes. Dev Neurosci. 2000;22(5-6):456-62. doi: 10.1159/000017475
55. Van Remoortel H, De Buck E, Compernolle V, Deldicque L, Vandekerckhove P. The effect of a standard whole blood donation on oxygen uptake and exercise capacity: a systematic review and meta-analysis. Transfusion. 2017;57(2):451-62. doi: 10.1111/trf.13893
56. Stellingwerff T, Morton JP, Burke LM. A framework for periodized nutrition for athletics. Int J Sport Nutr Exerc Metab. 2019;29(2):141-51. doi: 10.1123/ijsnem.2018-0305
57. Fry L, Madden AM, Fallaize R. An investigation into the nutritional composition and cost of gluten-free versus regular food products in the UK. J Hum Nutr Diet. 2018;31(1):108-20. doi: 10.1111/jhn.12502
58. Logan SW, Kipling Webster E, Getchell N, Pfeiffer KA, Robinson LE. Relationship between fundamental motor skill competence and physical activity during childhood and adolescence: A systematic review. Kinesiol Rev. 2015;4(4):416-26. doi: 10.1123/kr.2013-0012
59. Van Loon LJ, Tipton KD. Concluding remarks: nutritional strategies to support the adaptive response to prolonged exercise training. Nestle Nutr Inst Workshop Ser. 2013;75:135-41. doi: 10.1159/000345862
60. Gretchen V, Heather R. Position of the Academy of Nutrition and Dietetics: Dietary Fatty Acids for Healthy Adults Academy of Nutrition and Dietetics. J Acad Nutr Diet. 2014;114(1):136-53. doi: 10.1016/J.JAND.2013.11.001