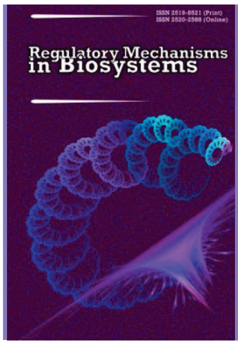

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Coadaptation mechanism of the gut microbiota and human organism to physical loading

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The human organism is home to trillions of bacteria, viruses and fungi. In order to survive, they have to adapt to the living environment of a host. The organism has adapted to mutual functioning by benefiting from microbiota in a certain way or removing its negative effects. The gut microorganisms influence all the organism systems, including the synthesis of heat-shock proteins. Their species composition and functional condition undergo changes depending on physical activity of a host organism. While moderate physical loading is of no doubt positive for the diversity of microbiota and the functioning of the intestinal barrier, the mechanism of influence of physical exercises on the microbiota biodiversity, its host and coadaptation is yet to be identified. *Lactobacillus acidophilus* bacteria were found to dominate in long-distance-track athletes who train endurance, while Bacteroidescoccae dominated in sprinter runners. Marathon runners were found to have many representatives of conventionally pathogenic Veillonella genus. They convert lactate into propionate and acetate – substrates for ATF formation. Bacteria generate an additional energy and increase the endurance of an athlete. At the same time, they cause inflammatory process in the host's gut. A temperature-increase effect is what the adaptation mechanisms to physical exercise and bacterial inflammatory process in the gut have in common. Rise in the temperature to a threshold value initiates an increased synthesis of heat-shock proteins, which regulate the function of the intestinal barrier by controlling high-density proteins. They are released from damaged or stressed cells and act as local "danger signals". Detecting molecular mechanisms of interaction between the gut microbiota and the human organism subject to physical exercise can be a valuable for identifying safe volumes and thresholds of training load and maintaining health.

Keywords: heat-shock proteins; alkaline phosphatase; short-chain fatty acids; gut microbiota; physical activity.

Introduction

The human gut is an environment for trillions of microorganisms. A combined genetic potential of endogenous microbiota is called microbiom. Microorganisms have evolved together with people and continue to live in them (Bäckhed et al., 2005; Wang et al., 2017). Genome richness of microbiota is one of the conditions of its successful coadaptation and coevolution with the human organism. Gut microbiota of an adult human is represented by thousands of various microorganisms. It acts as an additional endocrinous organ and is sensitive to homeostatic and physiological changes associated with training. Individual microbiota of the gut regulates the energy balance and participates in the control of inflammatory, redox processes and hydrotation (Donati Zeppa et al., 2019). Bacteria, archaea, fungi and viruses of the gastrointernal tract are called the gut microbiota. As humans evolved, microorganisms adapted to the host's environment in order to survive. At the same time, the host's organism has adapted to cofunctioning, learned to regulate the number and species composition, mitigate negative impacts and benefit from the "renters".

The microbiota takes part in the absorption of nutrients, biosynthesis of vitamins, enzymes, maturation of the immune system, resistance to colonization by pathogens and other critical physiological process (Ferreiro et al., 2018). It influences the central and enteric nervous systems (brain – intestine) through the immune system, vagus nerve, short-chain fatty acids, branched-chain amino acids and peptidoglycans (Cryan et al., 2019). The species composition of gut microorganisms changes subject to physical exercises and diets and can be an important tool for improving the general health and sports results. At the same time, the influence mechanism of physical activity on microorganisms of humans and animals has not been determined, making this review topic relevant. Around 95% of all the gut microbiota is considered commensal, and 5% belongs to the group of conditionally pathogenic microorganisms. If the host's defensive mechanisms weaken, all indigenous microflora starts to rapidly reproduce and disseminate throughout an organism. Through the mucous membrane, local gut bacteria enter the tissues and internal organs, and the process by which they do so came to be called bacterial translocation. Nature has compensated the weakness of the barrier epithelial monolayer by concentrating around 80% of all lymphoid elements in the intestine's region. They have an appearance of complex hierarchical networks with various types of cells. Furthermore, the gut has a highly active system of inherited immunity. Therefore, a couple of grams of IgA is secreted to the the gut lumen everyday, which is over 79% of all the production of antibodies (Vaishnavi, 2013).

Invasion of microorganisms occurs through cells, intercellular space, phagocytosis and defects in the intestinal epithelium. They accumulate in lymph nodes of the liver, lungs, spleen and perform the role of some kind of an exerciser for the immune system. In response to every bacterial strain, lymphocytes of the host produce specific antibodies and transform into memory cells. A trained organism is ready to encounter bacteria in the amount in which they cause a disease. During an inflammatory process, mechanical or thermal trauma, microorganisms enter the blood and lymph again. They cause local damage to the mucous membrane, dysfunction of the microvilli or damage to the coatings. The intestine is a reservoir for microorganisms, their endotoxins, peptidoglycans, and other toxic products. Disruption of the integrity of the intestinal barrier causes a systemic bacteremia and sepsis. The intestinal factors and/or bacteria can reach the blood circulatory system, where the liver is the first main organ that the microorganisms and their secretions encounter. At the same time, in the lymphatic pathway, they enter the systemic blood circulation at the level of the subclavian vein, and enter the pulmonary loop after passing through the heart. Therefore, on the route the intestinal lymph takes, the lungs are the first large vascular system that drains the gut (Deitch, 2012). Increased bacterial translocation can cause diseases. It was reported that ultrarunners often suffer infections of the upper respiratory pathways after training or competitions at peak of their fitness (Knechtle & Nikolaidis, 2018).

In the studies and reports conducted over the recent five years, the problem of interrelation of physical load and gut microbiota were studied through the lenses of disruption of the integrity of the intestine (Kim, 2021); mechanism of the microbiota's influence (Cataldi et al., 2022); specifics of use of lactate in the formation of propionate by Gram-positive microorganisms (Scheiman et al., 2019); oxidative stress (Donati Zeppa et al., 2019); heat-shock proteins and microbiota (Liu et al., 2022; Zahid et al., 2022); heat-shock proteins in adaptation and proliferation (Kuibida et al., 2021; Kuibida et al., 2022); the role of alkaline phosphotase (de Oliveira Dos Santos et al., 2021; Gao et al., 2022); permeability of the intestine, electrolytic dysbalance (Donati Zeppa et al., 2019); sensitivity to insulin (Fjære et al., 2019); specifics of pro-inflammatory profile (Zhao et al., 2018); dysbacteriosis (Yeoh et al., 2021), etc.

The objective of our review was to identify the mechanism of interrelation of gut microbiota, heat-shock proteins and other factors in the conditions of physical load, based on a literature analysis. The search for literature in the review was performed based on the abovementioned keywords in the electronic data bases PubMed and SPORTDiscus.

Influences of various types of moving activities on gut microbiota

The human organism has been colonized by symbiotic bacteria, weighing around 2 kg in total. Their species composition can vary depending on health condition and physical activity (Pane et al., 2018). The gut bacteria of humans mostly comprise Firmicutes (60–80% of all the gut bacteria) and Bacteroidetes (20–40%), and also a small amount of Proteobacteria and Actinobacteria. Athletes have a relatively small number of bacteria that produce short-chained fatty and dairy acids (Dziewiecka et al., 2022). As shown, the α-diversity of gut microbiota grows with age. By contrast, regular physical exercise causes changes in microbial composition and functions that are accompanied by the aging process. Regular physical exercise can significantly affect the composition and functioning of microbiota in elderly people with obesity (Zhu et al., 2020).

There are studies reporting that increase in the alpha-diversity of gut microbiota and a large number of several dominating *Bacteroides* bacteria increases the gut permeability. Bacteria of this genus produce enterotoxin that stimulates the degeneration of epitheliocytes of the human gut (Camilleri, 2019). Physical training has an effect on qualitative and quantitative differentiation of microorganisms that generate butyrate, including bacteria of the Clostridiales order or the Firmicutes phylum. The mentioned changes create the natural barrier that prevents pathogenic bacteria from invading the intestinal epithelium (Durk et al., 2018). There is no doubt regarding the positive effect of moderate physical load on the diversity of gut microbiota and functioning of the intestinal barrier. At the same time, intensive physical exercise with maximal aerobic strength (≥60–70% $VO_{2\,max}$) is not only harmful to the gastrointestinal system and microbiota, but also cause alteration of its structure and functionality. The permeability of the barrier for bacterial endotoxins and the infection of the entire organism has been reported (Gubert et al., 2020; Ruiz-Iglesias et al., 2020).

There was an attempt to identify the interrelation between the high cardiorespiratory effectiveness of an athlete and increase in the number of short-chain fatty acids in the intestine. Physical load with maximal aerobic strength ($VO_{2\,max}$) had a greater effect on the species diversity of microorganisms than age, sex or diet. Increase in the diversity of microbiota and production of butyrate are related to the general health of the host (Estaki et al., 2016). Women with low consumption of VO_2 oxygen were observed to have a decrease in the number of *Bacteroides* and increase in *Eubacterium rectale* and *Clostridium coccoides* in the phase before menopause (Durk et al., 2018). After a marathon run, an increase in the relative number of *Veillonella* was determined. Introduction of those bacteria made mice spend longer on the running track longer ? It has to be noted that microorganisms enter the gut lumen through the epithelial barrier and use lactate for propionate synthesis. Time of training on the running track was increased as a result of intrarectal administration of propionate. Therefore, the natural enzymatic process of synthesis of propionate or its administration improves sports results. Moreover, increased level of dairy acid promotes the colonization of the gastrointestinal tract by bacteria of the *Veillonella* genus (Scheiman et al., 2019). The level of negative impact of exercises on endurance was greater for athletes than subjects who were not engaged in sports (Krutsevich et al., 2021; Bonomini-Gnutzmann et al., 2022).

It was demonstrated that the leaky gut syndrome manifested after 60 min of intensive endurance training with 70% load of the maximal work capacity. Moderate physical training and dietary probiotics improved the gut health and composition of its microbiota. Increase in the time of performing exercises or increase in the intensity of physical exercises can cause a gastrointestinal syndrome – stomach pain, colic, tympany, nausea, vomiting or diarrhea. This syndrome affects 70% of athletes and occurs 1.5–3.0 times more often among qualified athletes than amateurs. During a long-distance run, the production of pro-inflammatory cytokines and proteins is boosted, initiating a systemic inflammation. Therefore, long-distance runners and triathlon athletes experience increases in the concentrations of toxic lipopolysaccharide; protein that binds fatty acids; interleukins IL-6 and 1β; tumor necrosis factor; γ-interferon; C-reactive protein. One of the commonest effects of this type of physical activity is increase in the intestinal permeability. In order to identify safe amounts and thresholds of training load for supporting health it can be important to detect molecular mechanisms that induce disruption of the integrity of the intestinal tract under the influence of physical exercise (Ribeiro et al., 2021).

Damaged mucous membrane and inflammations can be components of the mechanism of modulation of diversity of microbes in people who train endurance (Moitinho-Silva et al., 2021). Local intestinal ischemia accompanies the adaptation to physical load. It causes damages and impairments in cells through ATF synthesis in the respiratory chain of mitochondria (Liu et al., 2018), occurring in runners twice as often as in representatives of biking or swimming (de Oliveira et al., 2014). Therapeutic exercises caused no notable changes in the gut microbiota. By contrast, cardiorespiratory exercises can lead to initial changes in the gut microbiota. The indicated changes in the gut microbiome did not last during and after the period of the experimental intervention (Bycura et al., 2018).

Physical exercise can increase the number of bacteria that produce butyrate (*Roseburia hominis*, *Faecalibacterium pausnitzii* and Ruminococcaceae) (Mitchell et al., 2019). Changes in metabolism and composition of gut microbiota were studied in 73 soldiers under a prolong ed physiological stress. During a 4-day skiing exercise, the intestinal permeability increased by 62 ± 57% depending on a diet group. The increased intestinal permeability was related to increased inflammation. Against the backround of α-diversity, there occurred changes in the relative number (>50%) of identified genera of microorganisms. The indicated changes resulted from increased number of uncommon taxa and decrease in presence of dominating species of *Bacteroides* genus. Changes in the composition of gut microbiota were associated with 23% of fecal metabolites (Karl et al., 2017). There were studies of gut microbiome of a world-class ultramarathon runner before and after competitions in a 163 km mountain run during four time periods: 21 and 2 weeks prior to the run and 2 h and 10 days after. Two hours after the run, substantial changes were found in the gut microbiome of the ultramarathon runner. Alpha-diversity (Shannon Diversity Index) increased from 2.73 to 2.80, and bacterial composition at the phylum level (Firmicutes/Bacteroidetes ratio) increased from 4.4 to 14.2. Those changes at the macrolevel resulted from increase in the number of bacteria of the genera *Veillonella* and *Streptococcus* and decrease in *Alloprevotella* and *Subdolingranulum* (Grosicki et al., 2019).

In the intestine of marathon runners, an increase was seen in the number of representatives of potentially pathogenic genus *Veillonella*. Those bacteria convert lactate into propionate and acetate, which are substrates for the formation of ATF. Against the background of intensified energy formation, the endurance of an athlete is boosted, but at the same time, an inflammatory process in the intestine occurs (Scheiman et al., 2019). In another experiment, there participated 14 marathon runners, 11 ski athletes, and 46 sedentary healthy people comprising the control. The difference between the microbiota of the healthy people and marathon runners and skiers was 20 and 5 taxa respectively. The representatives of the experimental group had a low number of the main gut-microbiota genus *Bacteroidetes* and high number of *Prevotella* genus because of intestinal inflammations (Kulecka et al., 2020). Well-trained runners for average-length distances performed a week-long typical training and three-week intensive training. The amount of training was increased by 10%, 20% and 30% during each subsequent week. No significant changes were found in the alpha-diversity or overall microbial composition of the intestine of various groups of runners (Craven et al., 2022).

A study revealed that the gut microbiomes of 33 cyclists were represented by three taxonomic clusters with high representativeness of a) *Prevotella*; b) *Bacteroides*; c) mixtures of several genera – *Bacteroides*, *Prevotella*, *Eubacterium*, *Ruminococcus* and *Akkermansia*. A positive correlation was identified between the amount of training and the share of *Prevotella* bacteria in the athletes' microbiomes. Those microorganisms take part in metabolism of carbohydrates and aminoacids. It was determined that the number of *Methanobrevibacter* transcripts of professional cyclists was higher than in amateur cyclists (Petersen et al., 2017).

Microbiological studies were performed on 12 high-class martial arts athletes and 16 lower-qualification athletes. Microbial diversity and intestine diversity (Shannon Diversity Index equaled ($P = 0.019$) and the Simpson's Diversity Index ($P = 0.001$)) were higher in the professional athletes and were lower in the amateurs. The genera *Parabacteroides*, *Phascolarctobacterium*, *Oscillibacter* and *Bilophila* dominated in the professional athletes, and *Megasphaera* dominated in the lower-level athletes. Number of *Parabacteroides* genus positively correlated with the duration of exercise during an average-intensive week. The professionals were observed to have high diversity and metabolic ability of the gut microbiome. This could positively affect the sports results (Liang et al., 2019). The microbiota of the athletes with high training dynamics had high numbers of the following species: *Lactobacillus acidophilus*, *Prevotella intermedia* and *Faecalibacterium prausnitzii*. By contrast, the group of people with high dynamic and static components had a higher number of *Bacteroides caccae* bacteria (O'Donovan et al., 2020).

Physical training can lead to increase in the number of bacteria of the order Clostridiales and the genera *Lactobacillus*, *Prevotella*, *Bacteroides* and *Veillonella*. Those bacteria were found to dominate in the athletes requiring highest rate of oxygen consumption. *Lactobacillus acidophilus* bacteria dominated in athletes who had been engaged in endurance training, and Bacteroidescoccae dominated in sprint runners. Butyrate played a key role in the mechanism of interaction between host and microbiota. It modulates chemotaxis of neutrophils and strength of the immune response. By contrast, a maximal amount of consumed oxygen during intensive physical exercise inverse-correlated with biosynthesis of bacterial lipopolysaccharide. After entering the blood circulation system, lipopolysaccharide of the cellular wall of Gram-negative bacteria exerted toxic properties. It binds to the Toll-like receptor-4 of immune-competent cells and an inflammatory process occurs. At the same time, physical activity decreased the amount of lipopolysaccharide and stimulated the immune system (Mańkowska et al., 2022).

Research was carried out characterising the effect of fecal microbiota in the mechanism of response to short changes in the amount of training, from 32.6 ± 4.8 km/week to 11.3 ± 8.1 km/week in swimmers. It was demonstrated that simultaneously with change in amount of training, the structure of microbiota diversity was impoverished, decreases occurring in the shares of bacteria of the genera *Faecalibacterium* and *Coprococcus*. The provided data demonstrate the relationship between short term changes in the amount of training and the composition and structure of gut microbiota (Hampton-Marcell et al., 2020).

Role of heat-shock proteins and other factors in the coadaptation mechanism of microbiota and the human organism to physical load

Enteric microbiota is one of the main factors affecting the synthesis of heat-shock proteins (HSP) in the epithelial cells of the intestine (Liu et al., 2014). This is a class of proteins that form after increase in body temperature up to the threshold value. Regulation of the rates of their formation takes place at the stage of transcription under the influence of heat-shock factor (HSF). Light-heat-shock proteins are classified based on their molecular weight into HSP-72, 70, 60, 10 and others with the values of 72, 70, 60, 10 kDa, respectively. Research revealed that the mechanism of their action is based on the regulation of renaturation and intracellular transport of proteins, damaged by high body temperature or other factors. Functionally, they oversee other proteins, providing the normal functioning of active regulators, catalysers, transporters, etc and also process irreversibly damaged protein molecules.

Heat-shock proteins are candidates for the role of universal biological signalizers for several reasons. First of all, they are the commonest intracellular proteins, accounting for 10% of the total amount in a cell. They have been found in the nucleus, cytoplasm and mitochondria of the cells. Secondly, concentration of several HSPs increased up to 15% as a result of temperature rise, oxidative stress, deficit of glucose, chemical impact, ischemia-caused issues/reperfusion injury, ultraviolet emission, radiation, impact of infectous agents, and bacterial lipopolysaccharides. Thirdly, HSPs are old, higly conservative molecules, which were identified in almost each prokaryotic and eukaryotic organism. At the same time, an important signal of danger is that exogenous lipopolysaccharide has emerged later, is less common and is unique only for Gram-negative bacteria. Fourthly, HSPs have a high immune-modulating action. They are able to induce the peptide-specific immunity. Proteins of the families Hsp70 and Hsp60 can activate inherited immune response of a host, which activates maturation of dendritis cells and complement, and causes release of pro-inflammatory cytokines (Giuliano et al., 2014). The studies revealed that presence of *Mycobacterium tuberculosis* in the human organism initiates changes in the system of cyclic nucleotides and Ca^{2+} dependent regulatory processes (Demidov et al., 1990, 1991). One of the evidences of the HSPs' role in the response to stress was found in the experiment with rats and a cat, which were separated by a transparent acrylic glass. Visual impact of the cat caused significant increase in the generation of corticosterone and extracellular Hsp72 in blood serum of the rats. This reaction was absent in the adrenalectomied rats (Fleshner et al., 2004). There are several studies demonstrating increase in the level of Hsp72 in blood serum in patients after physical exercises (Lancaster & Febbraio, 2005; Whitham & Fortes, 2008).

Long intensive physical training can alter the species structure of microbiota, cause dysbacteriosis, inflammatory process, and lesions of the mucous membrane of the intestine. The common phenomena in the mechanisms of adaptation to physical exercises and inflammatory process of the intestine are the effect of increase in the body temperature and intensified HSP synthesis. In particular, physical load is accompanied by physical-biochemical changes and rise in the temperature of muscles above the threshold value of 38.5 ºC (Kuibida et al., 2022a). Heat-shock proteins provide renaturation processes and stabilize the tertiary structure of other important proteins – regulators, catalysers, transporters, which perform structural, defensive, receptory and mobile functions, as well as restore functions of proteins damaged by high body temperature or other factors (Kuibida et al., 2022). Thermal processing and pharmaceutical induction of HSP72 can prevent resistance of the skeletal muscles to insulin and intolerance to glucose. Excessive expression of HSP72 in the skeletal muscles caused 50% increase in the content of mitochondria and almost 2-fold increase in the ability to run and endurance (Archer et al., 2018).

Heat-shock proteins can strengthen the defense of the intestinal epithelium from oxidative stress (Viggiano et al., 2015). In particular, chaperones HSP27 and HSP70 can decrease the production of active oxygen species by activating glutathione reductase, peroxidase and other antioxidative enzymes (Doré & Blottière., 2015). Stress enhances synthesis of HSP70, and heat-shock protein inhibits the apoptosis of cells of the mucous membrane of the intestine (Wu et al., 2013). The studies found that mitochondria are the main target organelle for HSP70 in the protection of epithelial cells of the intestine from hypoxia/reoxygenation (Yuan et al., 2008).

In the defense of cells from high temperature or other forms of stress, HSP and molecules of the main complex of histocompatability are the two systems of presentation of peptide antigene (Binder, 2014). Heat-shock proteins regulate the function of the intestinal barrier by controlling high-density proteins. Intercellular space of the intestinal epithelial cells is naturally protected by them and is being continuosly reconstructed after impacts of microbes and antigens (Garrido et al., 2006). High-density proteins between the epithelial cells of the intestinal tract have an effect on maintenance of its barrier function. Expression of cytoprotectory heat-shock proteins HSP70 and HSP25 against the background of colitis was low. Gram-positive baceria *Lactobacillus reuteri* of the Lactobacillaceae family produce antimicrobial compounds, for example reuterin. It inhibits the growth of some bacteria, in particular: *Escherichia*, *Salmonella*, *Shigella*, *Proteus*, *Pseudomonas*, *Clostridium* and *Staphylococcus*, yeasts, fungi, protozoa and viruses. Strain 4659 of those bacteria provided a defense during experimental colitis, and intestinal HSPs conditioned probiotic effects. They provide protein-protein network of the epithelium in the healthy condition and during colitis (Liu et al., 2022). A decisive role in the regulation of permeability of the intestine belongs to the high-density protein occludin. A study demonstrated an important interaction between occludin and HSP70 (Zuhl et al., 2014). Under the influence of heat, the occludin concentration increased. The process was caused by activation of heat-shock factor-1 (HSF1) by binding with occludin gene promoter (Dokladny et al., 2008).

The system of protection of the stomach wall from lesions is comprised of several levels. The first level of the stomach mucous-membrane barrier has bicarbonates, mucus, immunoglobulins, antibacterial lactoferrin, and surfactant phospholipids. The second level of the defensive system is the stomach epithelium that is extremely resistant to acids and irritants. It forms a relatively strong barrier for a passive diffusion and recovers remarkably fast. The third level of the defense is microcirculation of the mucous membrane combined with sensory afferent nerves within the mucous membrane and submucousa. Back diffusion of acid or toxin into the mucous membrane induces the formation of peptide, associated with calcitonin gene. It increases the blood flow in the mucous membrane, reduces its lesion and enhances the recovery. The fourth level of the protection is provided by the immune system of the mucous membrane, represented by mast cells and macrophages. Heat-shock proteins are considered an additional factor of the defensive mechanism of the stomach at the intracellular level (Choi et al., 2009).

Expression of HSPs enhances four types of stimuli: 1) physical (radiation or heat shock); 2) chemical; 3) microbial irritants (pathogenic bacteria, viruses, parasites and fungi); 4) dietary. Some HSP functions in the immune system were determined in particular, 1) intracellular (presentation of antigene and expression of innate receptors); 2) extracellular (immune control of tumors and autoimmunity). Interaction between a virus and HSPs plays an aimportant role in the regulation of different stages of an infection – invasion of the cell and nuclear import, replication of virus and expression of genes, folding/assembly of viral protein, regulation of apoptosis and host's immunity (Bolhassani & Agi, 2019).

Reaction to heat shock, which is called reaction to stress, is the oldest, highly conservative, endogenous cellular defensive mechanism in which HSPs are involved. Extracellular HSPs are released from damaged or stressed cells and act as local "danger signals". They activate programs of responses to stress in the surrounding cells. Extracellular HSP27 stimulates secretion of anti-inflammatory cytokines, and HSP70 activates chemostasis of dendritic cells and neutrophils, stimulates monocytes, macrophages, and enhances the activity of macrophages. Absorption of eHSP70 improves the resistance to stress (Giuliano et al., 2014; Zahid et al., 2022). Induced heat-shock proteins (iHSP) are some of the most important systems of cytoprotectory defense of epithelial cells of the intestine. Once a heat stress occurs, they act in parallel with intestinal alkaline phosphatase (Harada et al., 2003).

Balance of phosphorylation/dephosphorylation of protein plays an important role in the regulation of proliferation and differention of cells. There are reports about decrease in density of the gut epithelial barrier, paleness of microbiota, dysbacteriosis, chronical inflammation of the intestine, and activation of intestinal phosphotase during aging (Kühn et al., 2020; Larrick & Mendelsohn, 2020). Stress alters the structure and activity of gut microbiota and causes dysbacteriosis in the intestine (Konturek et al., 2020). The main natural protector of epithelial cells of the intestine is the intestinal alkaline phosphatase. It detoxicates lipopolysaccharide of bacterial cell wall, exerts anti-inflammatory action and controls the compositions of gut microbiota. The enzyme catalyses breakaway of alkaline acid from proteins, alkaloids and nucleotides in an alkaline environment. Phosphatase decreases the toxicity of lipopolysacharide of the membranes of Gram-negative bacteria, causing poisoning and inflammatory process. Once one of phosphate groups is removed from lipid A (is included in the bacterial lipopolysaccharide), monophospholipid A forms. Its toxicity is 100 times lower than in the non-modified form. Therefore, phosphatase protects the organism from poisoning, inflammation and excessive bacteria entering blood and lymph (Gao et al., 2022).

Additives of intestinal alkaline phosphatase combined with moderate physical activity alleviate the severity of colitis and complicated obesity. Mechanism of the action of phosphotase includes inhibition of intestinal cytokine/chemokine network and oxidative stress, modulation of gut microbiota and improvement of muscle strength (Wojcik-Grzybek et al., 2022). Low physical activity, polluted air, toxins and antibiotics initiate the inflammatory process in the intestinal mucous membrane. Alkaline intestinal phosphatase and moderate-intensity physical exercises enhance the rates of recovery of an inflamated intestine (Bilski et al., 2020). Excessive running exacerbated the lesions of the large intestine in the obese mice. At the same time, there occured decrease in the microcirculation in the large intestine, increase in oxidative stress, and greater expression and activity of pro-inflammatory biomarkers (Bilski et al., 2019). The study revealed that exogenous intestinal alkaline phosphotase and sodium butyrate can be beneficial for alleviation of intestinal lipopolysaccharide-induced inflammation (Melo et al., 2016). Alkaline phosphatase is a prebiotic for the protection of child ren's guts from potentially pathogenic bacteria (Wu et al., 2022).

Regular physical exercise function as an anti-inflammatory means, inhibiting Toll-like receptors in immune-competent cells that recognize conservative structures of microorganisms. They activate monocytes, macrophages, neutrophils, eosinophils and other components of the cellular branch of the immune system to oppose a pathogenic impact of microbiota. Long or intensive physical exercise can be harmful to the immune system (Cavalcante et al., 2018). Intestinal phosphatase has become especially relevant because it supports the intestinal microbial homeostasis and the intestinal barrier, having the ability to de-phosphorilate microbial lipopolysaccharide (Santos et al., 2022).

Local and systemic production of cytokines in response to physical exercise is similar to the response of cytokines to infections, traumas and sepsis. After exhaustive physical exercise, increase in the level of bacterial lipopolysaccharide enhances the production of pro-inflammatory cytokines (Ghosh et al., 2015). In the participants of ultramarathons (duration of >6 h or >50 km), there occur microtraumas of the connective tissue, bones and skeletal muscles. Alterations occur in the structure and number of microbiota of the gastrointestinal tract and cells of the mucous layer die (Knechtle & Nikolaidis, 2018; de Oliveira Dos Santos et al., 2021). When the amount of physical exercise was excessive, there occurred increase in concentration of interleukin IL-6 (stimulates inflammatory processes) and decrease in IL-2 (inhibits inflammatory processes) and interferon. After a marathon, the level of IL-6 in blood plasma can increase 40-fold. A high level of interleukin can remain for 24 h (Gomarasca et al., 2020; Larsen et al., 2020; Skinner et al., 2021). Long induced metabolic activity and lesions of muscle cells are important triggers of migration of macrophages and neutrophils and release of cytokines (Alves et al., 2022). Moderate physical activity can be a beneficial physiological stressor. Negative impact of excessive physical exercises is caused by oxidative stress (Daniela et al., 2022).

Hypothetical models of mechanism of coadaptation of the gut microbiota and the human organism to long and high-intensity physical load

The mechanism of coadaptation of the gut microbiota and the human organism to physical load was observed to have both negative and positive effects.

During prolonged physical loading the human organism depletes its energy reserves of glycogene and available lipids; the pH environment undergoes changes; metabolites (lactate, active oxygen species, ketoacids and creatinine) accumulate; there occurs a rise in the temperature of muscles involved in contraction and relaxation, etc. The host organism and gut microbiota adapt together to homeostasis impairments. Microorganisms consume "compounds of fatigue" and a human's endurance increases. By contrast, physical load leads to changes in the species structure and functional activity of gut microbiota and some negative effects. There occur increases in concentrations of lipopolysaccharide of the bacterial walls, interleukins (IL-6, 1β), γ-interferone, and C-reactive protein. Against the background of ischemia of the instestine, the mucous layer undergoes inflammation, enterocytes die, and the permeability of the intestinal barrier and bacterial translocation increase. A short gastrointestinal syndrome manifests, which can lead to an array of diseases (Fig. 1).

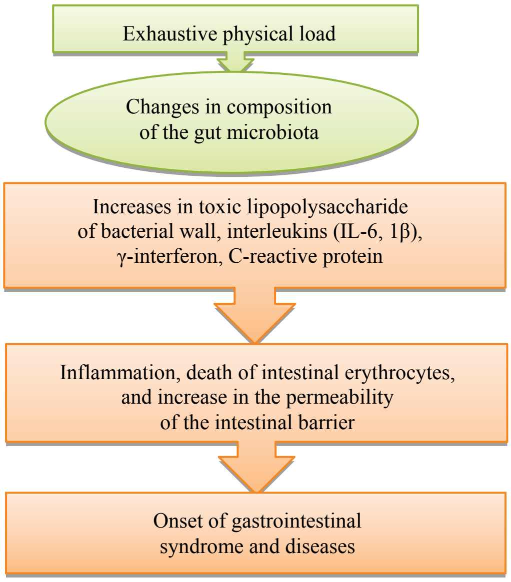

Fig. 1. Negative effects of relationship between an exhaustive physical load and the gut microbiota

During excessive load, lactate, the metabolite of fatigue, enters the intestine. The numbers of representatives of the potentially pathogenic genus *Veillonella* and others grow. Bacteria turn lactate into short-chain fatty acids: acetate, propionate and butyrate – substrates for the formation of ATF, boosting an athlete's endurance. On the other hand, the high level of lactate promotes colonization of the gastrointestinal tract by bacteria of the *Veillonella* genus. They cause inflammatory process in the host's intestine as a "price for a favour". Butyrate exerts anesthetic effect, thereby improving endurance. After a burst of training-related inflammatory stress during recovery, butyrate displays anti-inflammation effect (Fig. 2).

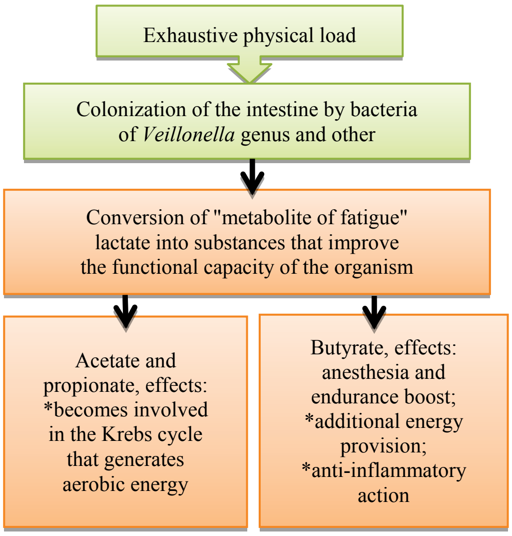

Fig. 2. Positive effects of interaction between exhausting physical exercises and the gut microbiota

Heat-shock proteins provide renaturation and stabilize the tertiary structure of other important proteins – regulators, catalizers, transporters, those performing structural, defensive, receptory, and mobile functions. Heat-shock proteins react to a combination of stressors: physical load, high body temperature (38.5 ºC), modified species structure of microbiota, bacterial lipopolysaccharide, oxidative stress, deficit of glucose and glycogen, lesions, ischemia/reperfusion, etc. Increase in the HSP concentration intensifies the synthesis of high-density proteins, activation of antioxidative enzymes, alkaline phosphatase and detoxication of lipopolysaccharide of bacteria, chemostasis of immune-competent cells, synthesis of cytokines for combating infections and post-training microtraumas, presentation of antigens and expression of innate receptors, immune control and weakening of apoptosis of intestinal enterocytes (Fig. 3).

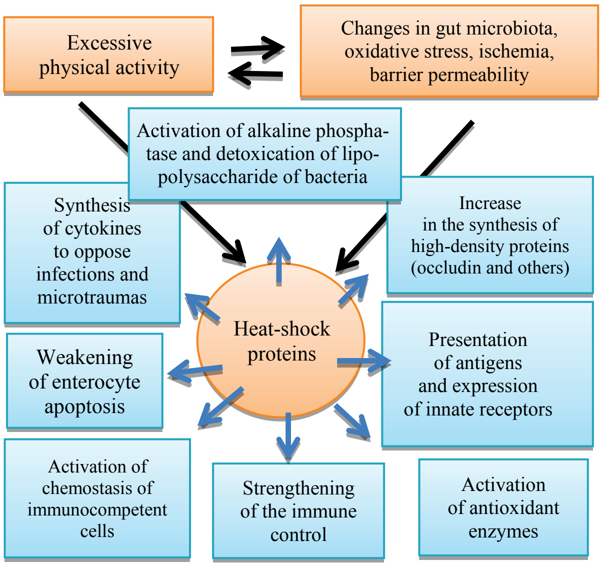

Fig. 3. Heat-shock proteins as an additional system of signaling and defense of the human organism in the system of interaction between physical activity and the gut microbiota

Conclusions

Gut microbiota influence the synthesis of heat-shock proteins, activity of alkaline phosphatase and all systems of the organism that are involved in the mechanism of adaptation to a physical load. Species composition and functional condition of microorganisms undergo changes subject to physical activity of a host organism. Moderate physical exercise increases diversity of microbiota, improves the metabolic profile, functioning of the intestinal barrier, and optimizes immunological reactions. No clear tendencies of influence of physical load on the gut microbiota were found during fast physical work, game sports, and martial arts. Against the background of excessive training, an increased amount of lactate enters the intestine, leading to increase in the numbers of representatives of potentially pathogenic genus *Veillonella* and others. Bacteria generate additional energy, boosting the endurance of an athlete, but at the same time cause inflammation in the host's intestine as a "price for the favour". Heat-shock proteins are released from damaged or stressed cells and act as local "danger signals". Alkaline phosphatase protects the organism from poisoning with lipopolysaccharide of Gram-negative bacteria, inflammation and high number of microorganisms entering blood and lymph. Identification of molecular mechanisms by which the integrity of the intestinal tract is breached under the action of physical exercise would be a serious ground for identifying dangerous amounts and thresholds of training load in order to support health.

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