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Original Article

Effect of Interleukin-2 on the humoral link of immunity during physical activity

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Abstract
The effect of physical activity can be considered as a prototype of stress with all the shifts in hormonal and immune systems that are inherent in the body's response to stress. The aim of this study was to evaluate the level of immunoglobulins during the process of adaptation to physical activity under conditions of stimulation and inhibition of interleukin-2 (IL-2). Five groups of mice were organized. Group 1 received an inhibitor of IL-2, Groups II, III and IV received IL-2 at concentrations of 5000, 7500 and 30,000 IU/kg, respectively, Group V received physiological saline only. The method of forced swimming was used as physical training. To determine the effect of IL-2 on humoral immunity during adaptation to physical training, blood levels of adrenaline, IgG, IgA and IgM were determined. In all groups anadrenaline concentration increased owing to physical activity. Furthermore, animals receiving IL-2 showed a higher level of adrenaline than animals in other experimental groups. This effect was dose-dependent. The IgG level increased in mice that received IL-2 while exercising. IgA and IgM levels remained independent of IL-2 stimulation, although the IgA level slightly varied in mice that received an inhibitor of IL-2. In all experimental groups IgA and IgM levels decreased irrespective of IL-2 stimulation and inhibition, the decrease was caused by physical training only. Blood tests of animals from all experimental groups showed a change in the ratio of immunoglobulins, that is an increase in the relative content of IgG during physical training and a decrease in the relative content of IgA and IgM.
Key words: cytokines, immunoglobulin G, immunoglobulin A, immunoglobulin M, adrenaline, physical stress.

Introduction

Maintaining health is a pressing issue today. Exercise and physical activity have numerous positive effects on the body (Levando, 2005; Nieman & Wentz, 2019; Terra, Silva, Pinto & Dutra, 2012; Wang & Boros, 2019). However, there are ambiguous results of research in the scientific journals on the effects of exercise on the human immune system.

According to the research results of V. Kozlov et al., high-intensity and long-term physical training had an adverse effect on the body and weakened the immune system (Kozlov & Kudaeva, 2002). The effect of physical activity can be considered as a prototype of stress with all the shifts in the hormonal and immune systems that are inherent in the body's response to stress (Simpson et al. 2020; Saraykin et al. 2019; Golovchenko & Gayday 2015). Numerous studies allow us to consider any changes in the immune system as a part of the classic stress response (Prokhorenko, Germanova & Sergiev, 2017; Hackeny, 2006; Sarapultsev & Sarapultsev, 2014; Shkuropat, 2016; Shvets, Hasiuk & Beschasniy, 2020). The sympathoadrenal system is immediately activated after exercise and so it results in increased adrenaline in blood serum, and approximately in 4-6 hours after exercise there is an increase in glucocorticoids (Kozlov & Kudaeva, 2002; Prokhorenko, Germanova & Sergiev, 2017; Gashi et al. 2020).

An increase in the concentration of these hormones leads to a redistribution of the cytokine network. Studies (Sarapultsev & Sarapultsev, 2014; Shvets & Hasiuk, 2019; Suzuki et al. 2002; Terra, Silva, Pinto & Dutra, 2012) have shown that after exercise there is an increase in the level of cytokines such as IL-4, IL-6, IL-10 and a decrease in IFNγ, IL-1, IL-2. It was found that exercise causes an increase in the number of neutrophils, a change in the subpopulation structure of lymphocytes, lymphopenia (Kozlov & Kudaeva, 2002; Terra, Silva, Pinto & Dutra, 2012; Wang, Liu., Li & Xiao, 2020). It leads to the suppression of the function and the deviation that is caused by the formation of Th2 with the production of the corresponding cytokines. There is a shift in the cellular immune response towards the humoral one. In the research paper (Nieman, 1996) it was shown that the formation of transient immunodeficiency is typical to intensive physical training, which is obviously associated with a decrease in Th1 and IL-2.

The results of the following researches (Abbas et al. 2018; Magherini et al. 2019) show that Th1 (CD3, CD4, CD45Ra) are activators of cellular immunity, cytotoxic T-lymphocytes, NK and monocytes, they also activate proliferation of B-lymphocytes that subsequently leads to an increase of IgG and IgM levels.

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According to the results of other researchers, the phenomenon of disappearing serum antibodies and immunoglobulins was found in athletes during intense training (Levando, 2005; Nieman & Wentz, 2019; Musin, Latukhov & Davletshin, 2008; Sokolenko, 2014). However, the authors of the study associated this phenomenon not with their reduced formation, but with changes in acid-base balance, body temperature and accumulation of intermediate products of metabolism in the blood, which caused fragmentation to subunits of complex structures of immunoglobulins.

Studies have identified IL-2 as an important cytokine involved in controlling immune responses and maintaining tolerance to its own receptors. It has been shown that the absence of IL-2 or blocking the transmission of its signal by receptors results in a numerous and / or functional deficiency of T-suppressors which causes autoimmune diseases (Tang et al. 2008; Abbas et al. 2018; Malek, 2008).

IL-2 performs effector functions and supports the formation of T-suppressors. The nature of the action depends on the concentration of IL-2 and its dynamics: a short-term action of IL-2 high concentrations stimulates the development of effector cells, and a prolonged influence of IL-2 low concentrations entails the development of T-suppressors (Tang et al. 2008; Alekhnovich, Ivanov & Livanov, 2011).

Research results point to the fact that physical activity leads to the phenomenon of disappearing antibodies in the serum after training (Pershin, Geliev, Churakov & Aleshkin, 2003; Wang & Boros, 2019). It may be caused by a change of the cytokine network under the influence of the adrenaline and cortisol hormones (Prokhorenko, Germanova & Sergiev, 2017; Hackeny, 2006; Gashi et al. 2020) since their higher concentration is observed after physical exercise. It is important to carry out a research of IL-2 influence on the number of serum immunoglobulins in order to identify immune response and to study the influence of IL-2 on the body's adaptation to physical stress as IL-2 is a key cytokine to triggering a cellular immune response.

The aim of the study was to assess the level of serum immunoglobulins during adaptation to exercise under conditions of stimulation and inhibition of IL-2.

Materials and Methods

The study was performed on white outbred adult mice with their total of 96 male mice weighing 29 ± 3 g, which were kept in standard vivarium conditions. The study adhered to the general ethical principles for the care and use of laboratory animals: "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 2005), "General Ethical Principles for Animal Experiments", adopted by the V National Congress of Bioethics (Kyiv, 2013).

The animals were divided into 5 experimental groups and one control group (without exercise) in order to determine the role of IL-2 in the adaptive processes. The animals of Group I received an inhibitor of IL-2 (Sandimmun Neoral Cyclosporine) 0.4 ml orally (concentration 10 mg / kg). Experimental Groups II, III and IV received the drug IL-2 (Roncoleukin, PJSC "Biotech") 0.2 ml subcutaneously in concentrations of 5000 IU / kg, 7500 IU / kg and 30,000 IU / kg, respectively. Group V was introduced sterile saline in equivolume. The drugs were administered 3 times a week before each workout. After 4 weeks there was a fourteen-day break from physical training. The study took 6 weeks. The method of forced swimming was applied as physical training. Every day one hour after drug introduction the method of forced swimming with a load of 7.5% of body weight was used to a complete exhaustion. This is the average aerobic-anaerobic level of exercise. Experimental mice were placed in a cylinder (h = 30 cm, d = 30 cm) filled with warm water (t = 25 ± 1 °C), where they swam until exhaustion. The load was secured in the intercostal space with a rubber band. The criterion of exhaustion was 3 unsuccessful attempts to swim to the surface or failure and sinking to the bottom.

The experimental study was conventionally divided into periods to determine adaptive changes (0, 2, 4, 6 weeks). The indicators of the control group were defined as 0 week of the study. IgG, IgA, and IgM analyses were made to determine the effect of IL-2 on the humoral part of the immune system during adaptation to exercise. Quantitative determination of the content of immunoglobulins in the serum was carried out using the method of competitive enzyme-multiplied immunoassay using a standard set of reagents "Ig A, M, G – ELISA" produced by "Granum". The determination of adrenaline concentration in blood plasma by Folin's method was applied to control the process of adaptation to exercise with the load. The method is based on the properties of phosphorus-tungsten and phosphorus-molybdenum mixture in the presence of adrenaline to recover with the formation of complexes colored blue. 0.2 ml of blood plasma, 4 ml of 10% sodium bicarbonate and 0.1 ml of Folin's reagent were added to the tube, and after 5 minutes spectrophotometer (wavelength 670 nm) against sodium bicarbonate. For the standard sample, the plasma was replaced with a solution of adrenaline. The amount of adrenaline was determined by the formula: (optical density of the test sample×100) / optical density of the standard solution.

To establish the differences between the experimental groups the Mann-Whitney test was used for unrelated samples whereas the Wilcoxon test was used for related samples.

Results

There are certain adaptation stages to physical training: the compensation phase, the decompensation phase and the recovery phase (Suzdalnitskiy & Levando, 2003). Therefore, the indicators of adrenaline and

serum immunoglobulins were studied according to the stages of adaptation to physical training: 2 weeks (compensation phase), 4 weeks (decompensation phase), 6 weeks (recovery phase).

Analyzing of adrenaline level in experimental mice demonstrated (Fig. 1) that stimulation of IL-2 in low concentrations led to a significant increase of adrenaline level in blood plasma compared to a control group ($p \leq 0.05$), the highest adrenalin level was registered at Week 4 of exercise with a further decline at Week 6.

Experimental animals receiving IL-2 in medium and high concentrations during exercise showed a moderate increase of adrenalin level in blood plasma in comparison with similar control indicators, which gradually increased during all phases of adaptation to exercise and peaked at 6 week of exercise ($p \leq 0.05$).

The group of animals receiving the IL-2 inhibitor during exercise showed an increase of adrenaline concentration in blood plasma at Week 4 with a subsequent significant decrease at Week 6, with a peak observed at Week 4 of exercise ($p \leq 0.05$).

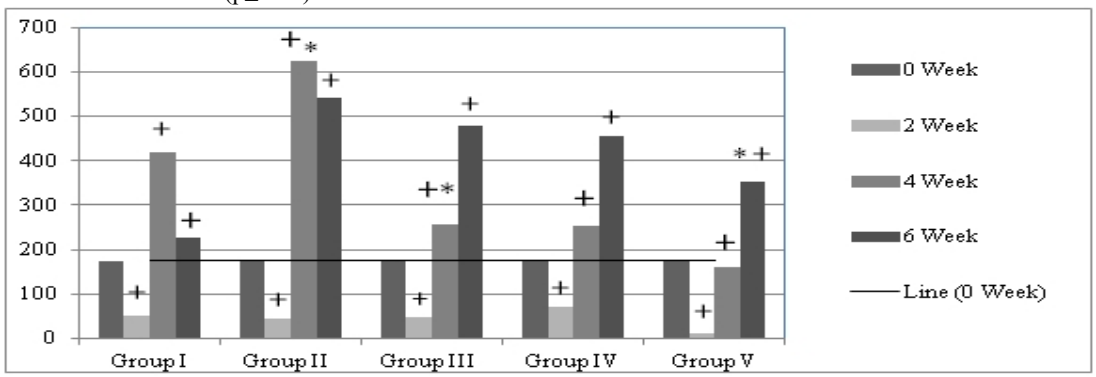

Fig. 1 – Adrenaline levels in the experimental groups, µg / l

Note: here and hereafter

\+ – the difference within the group compared to the previous period ($p \leq 0.05$);

* – the difference within a week between the indicators of different groups ($p \leq 0.05$);

Line - the level of the indicator in the control group.

The level of IgG in mice of Group I changed as follows: at Week 2 there was a slight increase of its content (by 1.4%) with a significant decrease at Week 4 (decrease by 3.9%; $p \leq 0.05$) and the actual restoration of the baseline at Week 6 of the experiment (Fig. 2).

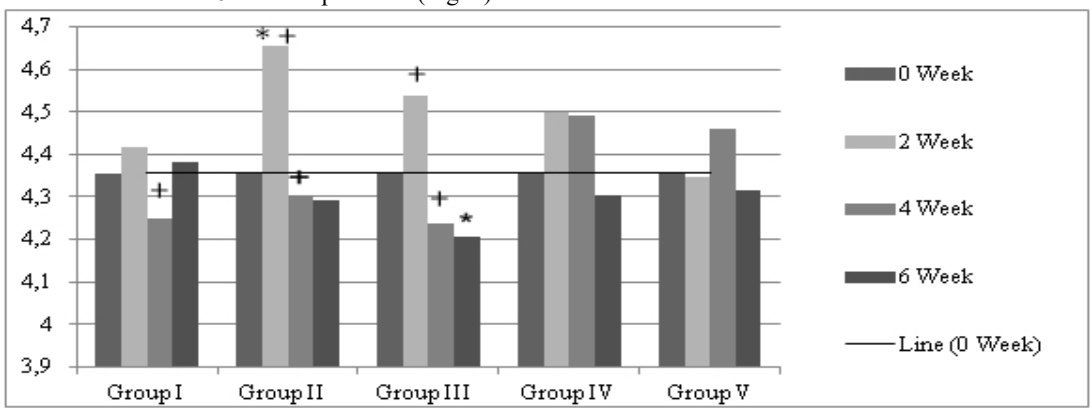

Fig. 2 – Indicators of immunoglobulin G in the experimental groups, g / l

Mice of experimental Groups II and III had similar fluctuations in the IgG level during the experiment and showed the following changes: at Week 2 the IgG level in the serum increased significantly compared to its baseline (by 6.7% – Group II, 4.2% – Group III ; $p \leq 0,05$), at Week 4 there was a significant decrease of its content ($p \leq 0,05$) with a subsequent insignificant decrease at Week 6. The mice of Group II demonstrated the highest IgG content at Week 2 compared to similar indicators in other experimental groups ($p \leq 0.05$). In Group III animals had the lowest decrease of IgG content at Week 6 among all experimental groups ($p \leq 0.05$).

The IgG content in the serum of mice that belonged to experimental Groups IV and V did not show any significant differences in the indicators of different weeks. In animals of Group IV there was a slight increase of IgG content at Week 2 of the experiment, at Week 4 the IgG level was almost unchanged, and at Week 6 it decreased slightly. In mice of Group V the IgG level was almost unchanged at Week 2 in comparison to a baseline, and at Week 4 it increased insignificantly with a slight decrease at Week 6.

The effect of IL-2 on the level of IgG in the serum during exercise was dose-dependent: the IL-2 low concentration caused the highest increase of IgG level at Week 2 of training (6.7%) with its subsequent decline during exercise (by 7.6 % at Week 4 and a further slight decrease of 0.3% at Week 6 of training). The medium

concentration of IL-2 increased the IgG level but it did not reach the IgG level of the group receiving IL-2 in low concentration (an increase of 4.2%) with a subsequent decline during exercise (a decrease of 6.7% at Week 4 and 0.7% at Week 6 of training). Mice receiving IL-2 in high concentration had a slight increase in IgG at Week 2 of training (3.3%). So, the lower the concentration of IL-2, the higher the increase in IgG at Week 2 of training.

Mice in the control group did not show any significant changes in IgG level during physical training, with only a slight increase at Week 4 of the experiment.

Mice receiving the IL-2 inhibitor did not show any significant fluctuations in IgG level during the entire period of exercise either. There was an insignificant increase at Week 2 (by 1.4%) with a subsequent decline at Week 4 (by 3.9%) and an increase at Week 6 (by 3.2%).

Consequently, a dose-dependent increase in IgG level under the influence of IL-2 at Week 2 of physical training (a compensation phase) and its decrease at Week 4 of training (a decompensation phase) was discovered: the lower the concentration of IL-2, the more significant the effect.

The IgA level was significantly reduced in all experimental groups at Week 2 of exercise ($p \leq 0.05$). In Groups I and V there was a decrease in IgA level at Week 4 of exercise (a decrease of 6.1% in Group I and 1.8% in Group V), while in mice of Groups II, III and IV there was a slight increase in IgA compared to the indicators of Week 2 (Fig. 3). In all experimental groups of mice, except Group II, at Week 6 of training there was a slight increase in IgA level comparing to Week 4, the above mentioned increase in Group I reached a level of reliability (an increase of 9.9%).

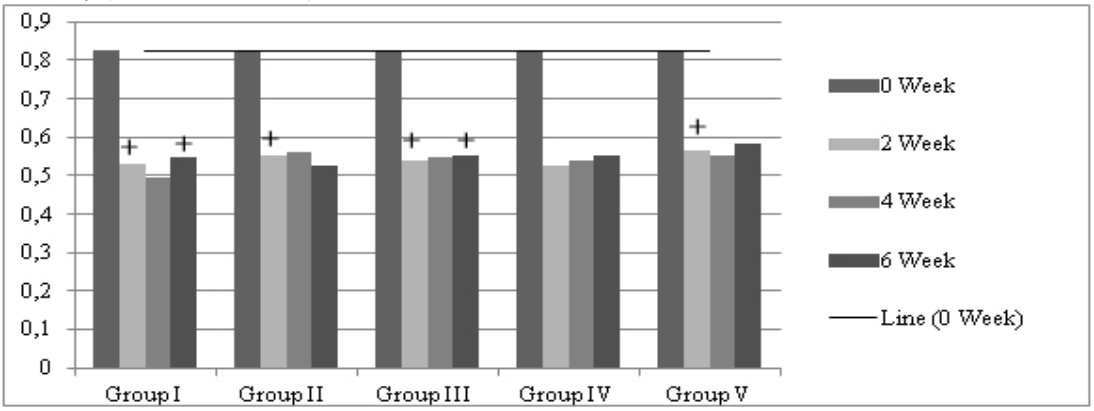

Fig. 3 – Indicators of immunoglobulin A in the experimental groups, g / l

Therefore, physical training caused a decrease of IgA level in all experimental groups at Week 2 of the experiment, and in groups of mice receiving IL-2 such a decrease was dose-dependent: the higher the IL-2 concentration, the more significant the decrease of IgA level. It should be stated that the level of significance of changes in IgA level during the following weeks of the experiment was reached only by mice receiving an inhibitor of IL-2 (a decrease of 33.9% at Week 2, a subsequent decrease of 6.1% at Week 4 and an increase of 9.9% at Week 6).

The IgM level as well as the IgA level at Week 2 of physical exercise reduced significantly in all experimental groups compared to a baseline ($p \leq 0.05$). In experimental Groups I, II and V at Week 4 there was an insignificant increase in the IgM level and mice of Group IV showed an insignificant decrease of the IgM level compared to the indicators of Week 2 (Fig. 4).

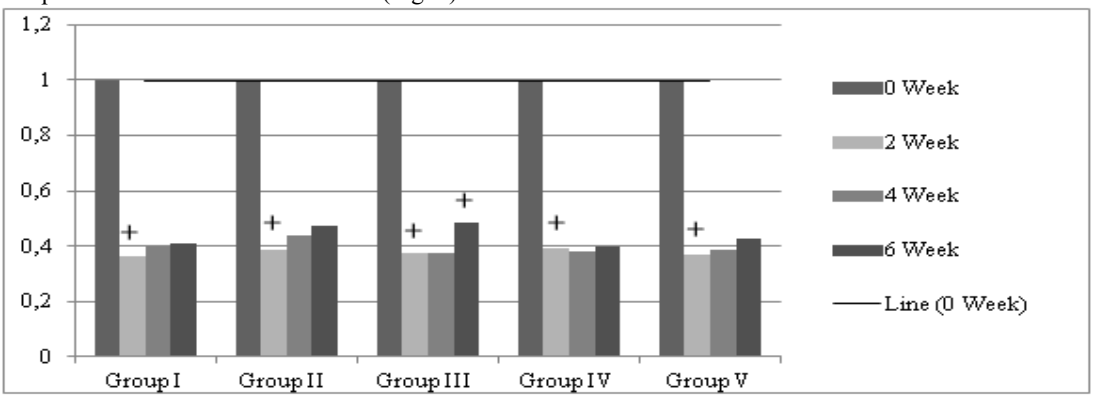

Fig. 4 – Indicators of immunoglobulin M in the experimental groups, g / l

Mice receiving IL-2 in low concentration showed an increase in IgM level at Week 4 (12.4%) and Week 6 (8.35%) in comparison with a significant decrease at Week 2 of training (a decrease of 61%). Mice introducing IL-2 in medium concentration showed a significant decrease in IgM levels at Week 2 (62.2%) and a significant increase at Week 6 (29.5%). Other experimental groups of animals showed a significant decrease in IgM level at Week 2 and a slight increase in its level in the following weeks of training.

In animals of all experimental groups, there was a change in the ratio of immunoglobulins, i.e. increasing of the relative content of IgG and decreasing of the relative content of IgA and IgM throughout the period of physical training (Fig. 5).

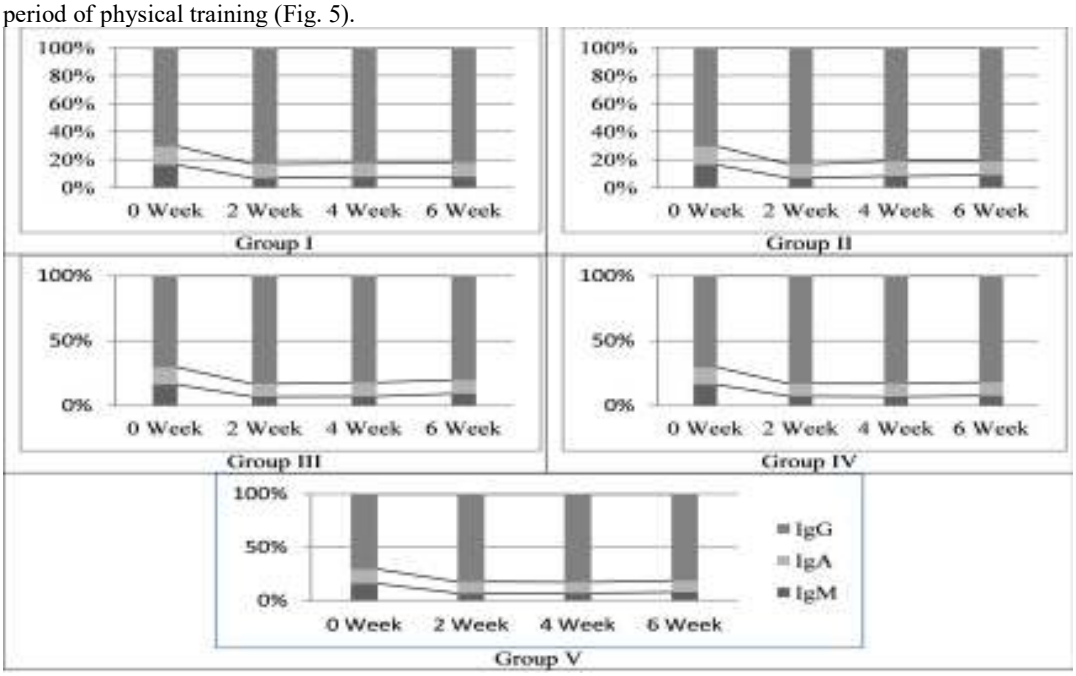

Fig. 5 – Normalized indicators of immunoglobulins A, M, G in experimental groups of animals

Thus, analyzing of adrenaline level in blood plasma showed that during the experiment its concentration increased under the influence of physical exercise in all experimental groups, so animals receiving IL-2 showed a higher level of adrenaline than the other groups did. This effect was dose-dependent. It is well-known that the concentration of adrenaline is an indicator of the body's adaptation to stress (Kozlov & Kudaeva, 2002; Prokhorenko, Germanova & Sergiev, 2017; Hackeny, 2006). So it is obvious that all experimental groups of animals were in the process of forming adaptation to physical activity.

It was found that IL-2 stimulation during exercise led to an increase in IgG concentration at Week 2 with a subsequent decline during a further physical training, as well as it led to a significant decrease in IgA and IgM levels at Week 2 (a compensation phase). Subsequently, at Week 4 and Week 6 the IgM level increased slightly, and the IgA level remained almost unchanged. This effect of IL-2 was dose-dependent: the lower the concentration introduced to mice, the more evident the changes in immunoglobulin levels.

The IL-2 inhibitor during physical exercise had almost no effect on IgG level and led to a significant decline in IgA and IgM levels at Week 2 (a compensation phase) as it was found in all experimental groups. At Week 4 there was even a greater decline in IgA level and its increase at Week 6, whereas the IgM level increased at Week 4 and Week 6.

The animals of the control group had only physical training and there were almost no changes in IgG level. The level of IgA and IgM, as in all experimental groups, decreased significantly at Week 2 of training and slightly increased by Week 6 of physical exercise.

In the compensation phase (Week 2), IgA and IgM levels decreased in all experimental groups, and it was apparently associated with physical training and almost did not depend on the effects of IL-2 and its inhibitor.

The IgG level was the most dependent on the IL-2 stimulation. Physical training and inhibition of IL-2 had no such effect.

Discussion

The decrease in the level of IgA and IgM at Week 2 of training coincides with the research results (Pershin, Geliev, Churakov & Aleshkin, 2003) on the phenomenon of disappearing immunoglobulins. Researchers associate this phenomenon with changes in acid-base balance, an increase in body temperature as a result of the accumulation of intermediate metabolic products in blood after exercise, and serve as a trigger for activating enzymes capable of fragmenting complex immunoglobulin structures into subunits (Pershin, Geliev, Churakov & Aleshkin, 2003; Sokolenko, 2014; Musin, Latukhov & Davletshin, 2008). The further gradual increase in IgA and IgM concentrations is apparently associated with an increase in alkaline blood reserve. The level of these immunoglobulins during exercise does not depend on the concentration of IL-2.

IL-2 is a cytokine that has a regulatory effect on Th1 and Treg. The nature of the action of IL-2 depends on its concentration and dynamics: a short-term action of IL-2 in high concentrations stimulates the development

of effector cells, a long-term action of IL-2 in low concentrations triggers the development of T-suppressors (Tang et al. 2008; Abbas et al. 2018; Malek, 2008).

Scientific studies (Levando, 2005; Hackeny, 2006; Nieman & Wentz, 2019) have shown that an increased activity of the sympathoadrenal system and the hypothalamic-pituitary-adrenal axis after physical exercise results in an increase of catecholamines and glucocorticoids in blood. IL-4, IL-6, IL-10 respond to physical activity. An increase of stress hormones leads to an increase of IL-6 and suppression of IL-2 function and / or a decrease of its receptors. Such a decrease of the IL-2 level leads to a decrease in the number of Th1 and an increase of the IL-10 content, which stimulates the formation of Th2 and shifts the immune response towards humoral one (Sarapultsev & Sarapultsev, 2014; Terra, Silva, Pinto & Dutra, 2012; Suzuki et al. 2002).
The pharmacological effects of rIL-2 are associated with its ability to activate clonal proliferation of T- and B-lymphocytes, to enhance the effector potential of cytotoxic cells (CTL-cells) and NK-cells, to increase the functional activity of mononuclear phagocytes and antigen-presenting cells, to increase the synthesis of specific immunoglobulins by plasma cells (Abbas et al. 2018; Terra, Silva, Pinto & Dutra, 2012; Shkuropat, 2018).

In the study (Alekhnovich, Ivanov & Livanov, 2011) it was shown that stimulation of the synthesis of specific immunoglobulins by plasma cells rIL-2 during immunocorrection triggered an increase in IgG and, meanwhile, had no effect on the content of IgA and IgM.

Researchers (Pershin, Geliev, Churakov & Aleshkin, 2003; Golovchenko & Hayday, 2016) have shown that immediately after physical activity a quantity of lymphocytes in the peripheral blood, their subpopulation structure and functional properties change. A significant number of indicators of the immune system return to baseline values in the first hours after physical training (Kozlov & Kudaeva, 2002; Zanini et al. 2018). However, after physical activity a number of lymphocytes remains below line for some time, it means that “transient immunodeficiency” is formed.

In our study it was shown that under the influence of IL-2 in low concentration there was a slight increase of IgG level after physical training compared with the control group, which performed only physical training. It happens as IL-2 stimulates clonal proliferation of B-cells and increases the synthesis of specific immunoglobulins by means of plasma cells. Therefore, these results can be applied for creating programs aimed at correcting the immune system in athletes during the preparation and competition periods.

Conclusions

It is for the first time that the effect of stimulation and inhibition of IL-2 on the level of adrenaline and serum immunoglobulins during physical activity adaptation was studied. Experimental groups recieving IL-2 were found to have a higher level of adrenaline during physical training than animals in other groups, and this effect was dose-dependent. In groups of mice that received IL-2 during physical activity, IgG level increased. The formation of IgA and IgM did not depend on the stimulation of IL-2, although the level of IgA varied slightly in the group receiving the IL-2 inhibitor. In all experimental groups there was a decrease in IgA and IgM levels, which did not depend on the stimulation and inhibition of IL-2, but only on the performance of physical activty.

The obtained results that show an increasing level of IgG as the result of stimulation of IL-2 during adaptation to physical activity can be used in training programs for athletes during their training period. As they often have a disappearing antibody phenomenon, the use of rIL-2 during physical activity can reduce the risk of colds and infectious diseases associated with this phenomenon.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and publication of thisarticle.

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