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Changes in the Plasma Levels of Myokines after Different Physical Exercises in Athletes and Untrained Individuals

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Abstract—The influence of dynamic and static load on the plasma level of myokines in strength-and endurance-trained athletes and untrained subjects has been studied. The range of myokines has been found to depend on the type of loads and the level of fitness. Dynamic and static exercises have different effects on the level of myokines in athletes and untrained subjects. The dynamic load increases the level of *IL*-6 and *IL*-8 in the plasma of athletes, while the static load increases the concentration of *IL*-15 and *LIF*. At the same time, no increase in the level of *IL*-8 after cyclic loading or in *IL*-15 after a static load has been observed in the control group. These differences may be based on a number of mechanisms. The cellular composition of skeletal muscles and the phenotypic features of muscle fibers, changing as a result of regular exercise, can modify the processes of myokine production. However, the processes of transcription in muscle fibers are much more important; the most important ones are *HIF*-1α, $[Ca^{2+}]_i$ and $[Na^+]_i/[K^+]_i$-dependent intracellular signaling pathways. The modification of these mechanisms caused by different physical loads and intensity is of great interest since it is a promising way to influence the metabolic processes at the cellular and systemic levels, which is very helpful in both improving athletic performance and correcting metabolic disorders in a number of socially significant diseases.

Keywords: myokines, interleukins, leukemia, inhibitory factor, dynamic and static exercise, athletes
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Skeletal muscles are part of the locomotor apparatus, provide for motor activity, and are involved in the processes of energy consumption and generation [1]. Numerous groups of investigators revealed [2–5] that physical exercises induce an increase in the plasma content of a number of cytokines, including the tumor necrosis factor *TNF*-α, the interleukins *IL*-1β, *IL*-6, *IL*-8, *IL*-15, and the leukemia inhibitory factor (*LIF*). At present, skeletal muscles are known to be the main source of *IL*-6 production, which accounts for its exercise-induced increase in blood plasma [6]. The *IL*-6*mRNA* transcription in the nuclei of muscle cells isolated from human muscle biopsy specimens after the performance of a single exercise was revealed [7]. Murine *C*2*C*12 myoblast cultures and primary human myotubes subjected to electrical stimulation (EPS) were also used to study myokine production by muscle cells. EPS is widely used for simulation of the muscle contraction model in vitro to study myokine production by muscle cells [8–10]. Using this approach, it was shown that 24 h after EPS, the production of 183 differentiated transcriptional factors and an increase in the secretion of *IL*-6, *IL*-8, the chemokine *CXCL1,* and *LIF* occurs in human myotubes [11].

The current investigations show that skeletal muscles as an endocrine organ are capable of producing cytokines and other peptides [12]. In the opinion of many researchers, these compounds can be classified as myokines, which exert various physiological effects on the body [13–15].

IL-6 is one of well-known inflammatory cytokines. It is synthesized by activated monocytes/macrophages, fibroblasts, and endothelial cells in inflammation, traumas, hypoxia, and exposure to bacterial endotoxins [16]. The biological role of *IL*-6 primarily consists in induction of restorative mechanisms and activation of immune defense. In addition, a suppressive effect of *IL*-6 on the inflammatory reaction by inhibiting the synthesis of the tumor necrosis factor (*TNF*α) is also known [17].

At present, the role of *IL*-6 in the regulation of metabolism has been established. In adipose cells, *IL*-6 increases oxidation of fat, as well as stimulates the secre-

Anthropometric data of the participants in the study ($X_{mean} \pm m$)

Group	Age, years	Height, cm	Body mass, kg
WL (weightlifting)	19.9 ± 1.4	177.0 ± 4.5	82.7 ± 10.2
TF (track and field athletics)	20.8 ± 1.4	180.2 ± 6.2	73.2 ± 6.9
CG_1 (control)	19.5 ± 0.7	183.2 ± 5.7	74.5 ± 4.75
CG_2 (control)	20.2 ± 1.1	179.4 ± 3.1	69.8 ± 3.1

tion and activity of lipoprotein lipase. In hepatic cells, *IL*-6 aids in the release of glucose and stimulates the breakdown of glycogen [15].

On the contrary, in muscle cells, *IL*-6 increases the effects of insulin and stimulates the utilization of glucose. During physical exercises, *IL*-6 acts as a mediator of glucose production. The studies also showed that *IL*-6 could activate *AMPK* for stimulation of lipolysis and oxidation of lipids [13]. Thus, *IL*-6 produces endocrine effects providing for increased energy production via increased glucose production in the liver and stimulation of lipolysis in adipose tissue [18].

IL-15 decreases the deposition of lipids in the preadipocytes and the mass of white adipose tissue [19]. *LIF* induces the proliferation of the cells thought to contribute to muscular hypertrophy and regeneration [20, 21]. Therefore, the role of interleukins and other myokines in the pathogenesis and therapy of metabolic disorders and the cardiovascular system, pulmonary, and locomotor apparatus diseases is being discussed at length [13, 22].

It should be noted that most of the myokine production data were obtained in the studies using cyclic exercises, while the data on myokine production during isometric exercise are limited to few works [23–26]. It is noteworthy that in cyclic (aerobic) exercises, such as walking, running, and swimming, large groups of muscles accounting for more than two thirds of the total musculature are involved. As distinct from cyclic exercises, strength and isometric exercises usually involve local groups of muscles making up less than one third of the total musculature.

During isometric exercises, the length of muscles does not change, which also distinguishes them from loads of dynamic character. Static muscular exercise causes more rapid fatigue development, because it does not include the relaxation phase, during which it is possible to supplement energy resources expended for muscular contractions [27]. We did not find any studies of the influence of preliminary training on myokine production in static and dynamic exercise. In addition, it is important to consider the individual features of changes in the level of plasma myokines after physical exercise. Data are known that the plasma content of protein IL-6 of 200 participants in the Western States 160-km Endurance Run marathon varied between 5 and 800 pg/mL [28].

In this connection, the aim of this study was to investigate the influence of dynamic and static exercise on the plasma myokine content in athletes of strength and cyclic kinds of sports, as well as untrained volunteers.

METHODS

Healthy young men whose ages varied between 18 and 23 years were enrolled in the study. The main group 1 included 10 professional weightlifters (WL). The main group 2 included 10 track and field (TF) athletes specializing in middle-distance running. The athletes from the main groups 1 and 2 had been engaged in their kind of sport for more than six years. The anthropometric data of the athletes are shown in the table. An athletic category not inferior to the Master of Sports title was a necessary requirement for enrolment in the study. The control group consisted of 20 subjects who were healthy untrained volunteers not engaged in sports. The control group was divided into two subgroups of 10 subjects. Subgroup 1 (CG1) volunteers performed static exercises; subgroup 2 (CG2) volunteers, dynamic exercises. At the time of the study, none of the subjects had a history of acute and chronic diseases. The participants were explained the aim of the study. All of them signed an informed consent to take part in the investigation and to have their blood sampled. The performance of the study was approved by the Ethics Committee of the Tomsk State University (registration no. 11 of September 24, 2015).

Weightlifter athletes (TA) and volunteers (CG1) performed a single grip at a below-the-knees level as a static exercise. All the weights constituted 50% of the maximal result shown in the deadlift exercise. The maximal weight was determined beforehand, not later than a week prior to the study. The maximal weight determination procedure was preceded by warming up and instructing how to perform a load exercise. A professional coach supervised the process and instructed the subjects. All the subjects had a vigorous warm up before the static weight-holding exercise. Exercise performance was also supervised by the instructor. The weight was to be held until the state of complete fatigue was felt and it was no longer possible to continue the exercise. The grip time was kept with a stopwatch. A doctor watched the subjects' condition.

The standard *PWC*170 test technique was used as dynamic load for weightlifter athletes (TF) and volun-

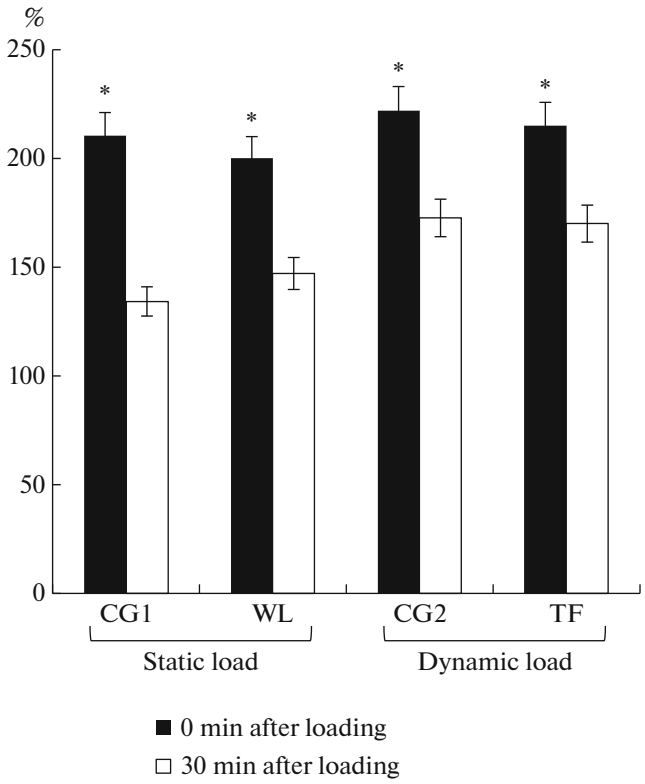

Fig. 1. Change in the lactate level after physical exercise. * Statistically significant changes in relation to the preload value at $p < 0.05$.

teers (CG2) [29]. The test was performed without preliminary limbering. The test included two-stage loading with a varying power. The first stage included exercising on a bicycle for 5 min with a power adjusted to the subject's body mass with tables. The heart rate (HR) was measured 15 s before the end of loading. At the second stage, the subjects had a 3-min rest. The third stage included pedaling the exercise bicycle for 5 min with a power adjusted to the HR at the end of the first load using tables. The HR measurement was performed 15 s before the end of loading.

Blood (5 mL) was sampled using the BD Vacutainer® vacuum system (Greiner Bio-One, Austria) three times (before loading, sample A; immediately after loading, sample B; 30 min after loading, sample C). The choice of the time intervals for blood sampling was determined by the fact that, according to the literature data, myokine production could increase both immediately during exercise [30] and after certain time intervals upon completion of exercise [11].

All volunteers underwent examination on an empty stomach in the morning. The athletes were recommended that the training process be stopped one day prior to the study. Vacuette® test tubes (Greiner Bio-One, Austria) with lithium heparin and a barrier gel volume of 5 mL were used. The heparin concentration in the test tubes was 20 U/mL. The blood samples were centrifuged for 30 min after blood withdrawal using a laboratory LMC 3000 centrifuge (Biosan, Latvia). Centrifugation was carried out for 11 min at 2000 rpm. The plasma was frozen and stored in a deep-freeze compartment at –20°C; the shelf life did not exceed 30 days.

The plasma protein concentration was determined using the enzyme-linked immunosorbent assay (ELISA). Platinum ELISA kits with antibodies directed against the corresponding proteins: Human LIF Platinum ELISA Kit, Human IL-6 Platinum ELISA Kit, Human IL-8 Platinum ELISA Kit (eBioscience, Austria), as well as RayBio® Human IL-15 ELISA Kit (RayBio®, United States), were used with instructions attached to the kits. All the samples were poured in two replicates. Flat-bottom immunological plates with 96 wells (the plate size is 12 × 8 wells) were used for the assay. Incubation was carried out on a PST-60HL thermal shaker for plates (Biosan, Latvia). The washing procedure was performed using the Anthos Fluido 2 washing device (Biochrom, United Kingdom). The optical density of the samples was measured with an Anthos 2010 microplate spectrophotometer with filters (400–750 nm) and the ADAP+ software package (Biochrom, United Kingdom). Serial dilutions of highly concentrated protein solutions attached to the kits were used for preparation of the standards. The optical density of the samples was calculated at 450 nm; the reference wavelength was 620 nm.

The lactate concentration in the capillary blood was measured using an Accutrend Plus portable device (Roche Diagnostics, Germany).

The data were statistically processed using the Statistica 8.0 software package. The normality of distribution of characteristics in the groups was assessed using the Shapiro–Wilks test. Comparative analysis of independent and dependent samples was made using the Mann–Whitney and Wilcoxon's test, respectively. The value $p < 0.05$ was taken as a criterion of a statistically significant difference.

RESULTS

In all the groups, the blood lactate level was found to increase after static and dynamic loading. A 2.2-fold increase was observed in the track and field athletics group. In weightlifters, the blood lactate increased twofold after static exercise. In the control groups, 2.1- and 2.3-fold increases were observed after static and dynamic loads, respectively. After 30 min, restoration of lactic acid to the initial level was observed in all the groups. The results of a change in the venous blood level of lactate are shown in Fig. 1. These results lead us to consider that the level of load in all the subjects was the same and it is the character of loading and the character of preliminary training that account for differences in myokine production.

The influence of static load on myokine production. In the group of weightlifters, an approximately 25%

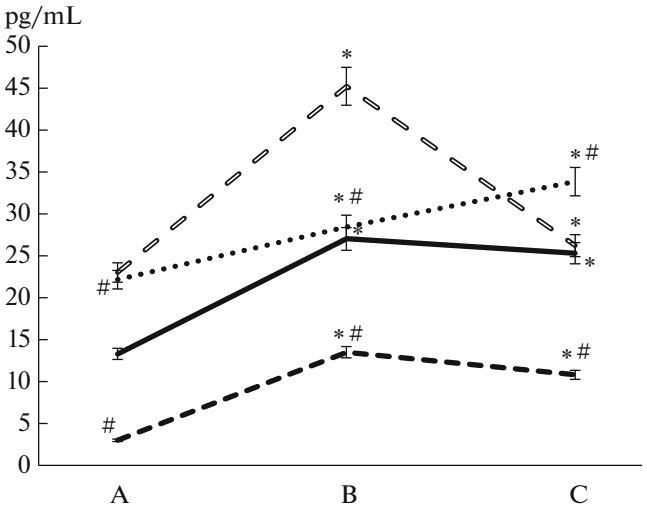

Fig. 2. Plasma concentration of *IL*-6 at rest and against the background of physical exercise. Solid line, control group 1; dotted line, the weightlifting group; double broken line, control group 2; broken line, track and field athletics group; A, before loading; B, 0 min after loading; C, 30 min after loading; * $p < 0.05$ compared with the blood sample A; # $p < 0.001$ compared with the control.

increase in the plasma *IL*-6 concentration occurred after static load. Note that in CG1, the *IL*-6 content after static load increased twofold (Fig. 2). In the athletes, the plasma content of *IL*-6 remained increased 30 min after exercise performance.

After static exercise, an insignificant increase in the plasma concentration of *IL*-8 (from 109.93 ± 1.63 to 123.29 ± 2.92 pg/mL) in athletes was observed, whereas in CG1, the static effort was followed by a 25% decrease in the *IL*-8 level (Fig. 3).

The *IL*-15 concertation considerably increased (by 47.4%) in athletes after a static effort (Fig. 4). Note that in the control group, no considerable increase in the content of this protein was found after static exercise (38.96 ± 2.52 and 42.31 ± 1.75 pg/mL). An increased plasma level of *IL*-15 persisted after 30 min of static load in weightlifters.

In weightlifters and untrained subjects, static exercises resulted in a ~60 and 30% increase in the plasma concentration of *LIF*, respectively (Fig. 5). It should be noted that, 30 min after the exercise, the plasma concentration of *LIF* in the control group increased from 6.12 ± 1.99 to 7.69 ± 1.13 pg/mL, while in the athletes, this value decreased from 12.24 ± 1.66 to 6.82 ± 1.68 pg/mL ($p < 0.05$), i.e., virtually to the initial value (7.73 ± 1.77 pg/mL).

The influence of dynamic load on myokine production. On completion of dynamic exercise, the plasma *IL*-6 content increased more than fourfold in track and field athletes (Fig. 2), but its concentration (13.50 ± 1.63 pg/mL) was substantially lower than in CG2, i.e., in volunteers who performed a similar dynamic exercise (45.25 ± 1.26 pg/mL). After 30 min, the plasma content of *IL*-6 was completely normalized in the volunteers who performed the dynamic exercise.

In track and field athletes, an approximately twofold increase in the plasma concentration of *IL*-8 was found after dynamic loading; however, dynamic load did not exert a considerable influence on the protein concentration in CG2 (Fig. 3). In the group of track and field athletes, the *IL*-8 concentration decreased approximately twofold 30 min after loading, while, in other groups, its level decreased by less than 25% (Fig. 3).

In contrast to static load, exercises of cyclic character did not exert an appreciable influence on the

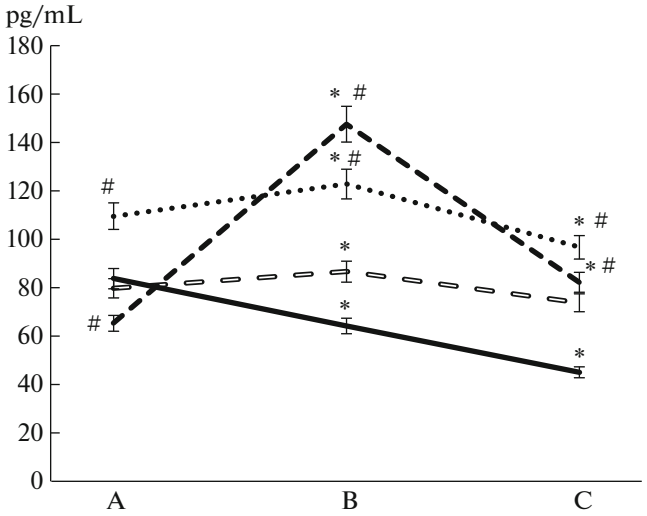

Fig. 3. Plasma concentration of *IL*-8 at rest and against the background of physical exercise. See Fig. 2 for the designations.

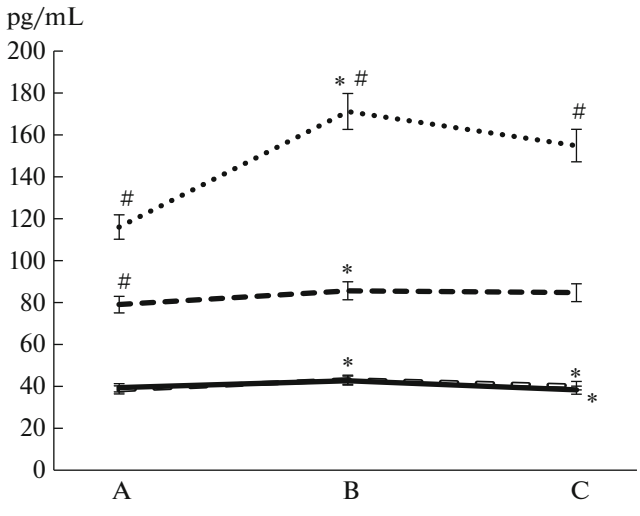

Fig. 4. Plasma concentration of *IL*-15 at rest and against the background of physical exercise. See Fig. 2 for the designations.

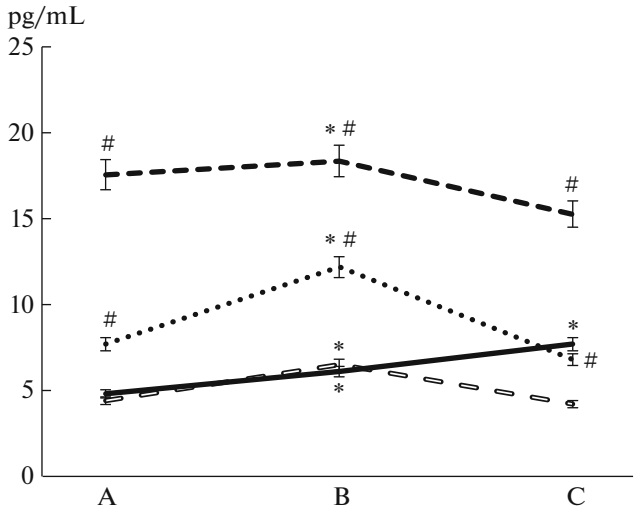

Fig. 5. Plasma concentration of *LIF* at rest and against the background of physical exercise. See Fig. 2 for the designations.

change in the *IL*-15 level in the track and field athletics group and in the control group (Fig. 4). Dynamic exercises did not exert a significant influence on a change in the plasma concentration of *LIF* in track and field athletes, whereas in the control group, the increase after dynamic load was approximately 35% (Fig. 5).

DISCUSSION

The results obtained allow us to make two main conclusions. First, the influence of static and dynamic exercises on the plasma cytokine content differs significantly. Long-term dynamic exercises cause the athletes' plasma content of *IL*-6 and *IL*-8 to increase, which agrees with a number of publications [5, 6, 31]. In contrast to dynamic loads, static ones exert little influence on the content of these cytokines in strength-trained athletes (Figs. 1, 2). At the same time, endurance-training exercises did not substantially influence the *IL*-15 and *LIF* concentrations, while static load resulted in a 50% increase in the plasma level of these cytokines (Figs. 3, 4).

Second, both dynamic and static exercises influence differently the plasma cytokine content of athletes and untrained subjects. For example, the athletes exhibited a twofold increase in the plasma concentration of *IL*-8 after a cyclic load, while this response was absent in untrained individuals (Fig. 2). No plasma *IL*-15 increase induced by static load in the weightlifters was observed in the control group (Fig. 3). These facts can be accounted for by the adaptation changes caused by regular physical loads in the body of athletes [13, 28].

The specific features of the influence of dynamic and static load in myokine production in athletes and untrained young subjects may be related to differences in the cellular composition of muscles. The skeletal muscle is very heterogeneous; in addition to myocytes, it contains a number of cells such as fibroblasts, pericytes, adipocytes whose contribution to the total volume of cytokine production was ill-defined [28]. The relative contents of these cells, as well as their effects on the cytokine production caused by physical load, may be different in athletes and untrained individuals. In addition to tissue heterogeneity, skeletal myocytes were shown to be subdivided into three different phenotypes each of which has its specific features of bioenergetic mechanisms [32].

Another mechanism providing the differences described may be connected with the features of the transcription mechanisms. Transcription changes in contracting muscles were shown to be most marked in quickly contracting type IIa muscle fiber [33], which, undoubtedly, affects the rate of myokine production.

Hypoxia-inducible factor-1α (*HIF*-1α), cAMP- and Ca_i^{2+}-dependent phosphoprotein kinases, as well as the monovalent cation concentration ratio ($[Na^+]_i/[K^+]_i$), afford signaling and are involved in excitation transcription coupling in skeletal muscle cells [34, 35]. *HIF*-1α is translocated into the nucleus where it forms the *HIF*-1α/*HIF*-1β complex and transcription triggers for dozens of genes, including the vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) [36]. It is important to note that, in contrast to dynamic load, strength-training exercises cause vascular occlusion and local hypoxia, which is accompanied by the accumulation of VEGF and eNOS mRNA in rat skeletal muscle [37]. However, the role of this pathway in the regulation of cytokine production has not yet been studied in detail.

The role of *AMPK* in exercise-induced myokine production is confirmed by the data indicating that *IL*-15 production was decreased in mice depleted of the *AMPK* β1 and β2 subunits in skeletal muscles [38]. *AMPK* phosphorylation increases in the muscles of strength-trained athletes after exercising on a bicycle, but no such response was revealed in endurance-trained athletes [26]. However, it should be noted that *IL*-6 gene expression in contracting muscle was normal in knockout *AMPK* α2-depleted mice [39].

An increase in the extracellular calcium concentration from ~0.1 to 1 μM in contracting muscle influences the expression of many genes, i.e., an important factor of initiation of the transcriptional mechanisms [34, 40, 41]. The injection of the Ca^{2+} ionophore ionomycin into rat soleus muscle for one hour results in a fivefold *IL*-6 mRNA increase [42]. Exposure of *C2C12* myoblasts to the Ca^{2+} ionophore *A*23187 sharply increased *IL*-6 mRNA transcription [43]. Using the same in vitro exercise model, it was shown that EGTA, a specific chelator for extracellular Ca^{2+},

decreased twofold the accumulation of *CXL* upon electrical stimulation [44].

Myocyte excitation is accompanied by changes in the transmembrane gradient of monovalent cations due to Na^+ inflow and K^+ outflow via potential-dependent and Ca^{2+}-sensitive ionic channels. In the muscle cells of humans and experimental animals, long-term exercises result in a three- to fourfold increase in $[Na^+]_i$ and a 50% decrease in $[K^+]_i$, which is accompanied by the $[K^+]_i$ increase in plasma and intercellular fluid [45–49]. This allows the conclusion that elevated $[Na^+]_i/[K^+]_i$ ratio is a factor stimulating myokine production [35]. In some types of cells, the increase in the $[Na^+]_i/[K^+]_i$ ratio led to mRNA expression in a number of cytokines, including *IL*-6 [50].

To assess the relative contribution of Ca_i^{2+}-mediated and Ca_i^{2+}-independent signaling pathways, we compared transcriptomic changes when the $[Na^+]_i/[K^+]_i$ ratio elevated in calcium-depleted cells and revealed an increased number of specific $[Na^+]_i/[K^+]_i$-sensitive genes [48]. The myokine *IL*-6 gene was revealed among $[Na^+]_i/[K^+]_i$-sensitive genes activated irrespective of the presence of Ca^{2+} chelates. Recently, it has been revealed that extracellular Ca^{2+} chelates considerably increase membrane permeability for monovalent ions, which results in the elevated $[Na^+]_i/[K^+]_i$ ratio [51]. We have also shown that, in the vascular smooth muscle cells, hypoxia-triggered transcriptomic changes are at least partially induced by *HIF*-1α-independent, $[Na^+]_i/[K^+]_i$-mediated excitation-transcription coupling [52].

CONCLUSIONS

Summing up the results, it should be noted that the range of myokines depends on the type of loads and the level of fitness. Dynamic and static exercises have different effects on the level of myokines in athletes and untrained subjects. The dynamic load increases the level of *IL*-6 and *IL*-8 in the plasma of athletes, while the static load increases the concentration of *IL*-15 and *LIF*. At the same time, no increase in the level of *IL*-8 after cyclic loading or *IL*-15 after a static load was observed in the control group.

These differences may be based on a number of mechanisms. The cellular composition of skeletal muscles and the phenotypic features of muscle fibers, changing as a result of regular exercise, can modify myokine expression. However, the processes of transcription in muscle fibers are much more important; the most important ones are *HIF*-1α, $[Ca^{2+}]_i$ and $[Na^+]_i/[K^+]_i$-dependent intracellular signaling pathways. The modification of these mechanisms caused by different physical loads and intensity is of great interest as it is a promising way to influence the metabolic processes at the cellular and systemic levels, which is very helpful in both improving athletic performance and correcting metabolic disorders in a number of socially significant diseases.

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