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EFFECTS OF VARIOUS AVERSIVE ENVIRONMENTS ON OXYGEN CONSUMPTION OF MUSCLE AND BLOOD IN MICE UNDER CONDITIONS OF THE "FORCED SWIMMING" TEST

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The aim of the study is to assess the effect of various aversive environments on the oxygen consumption in muscles and blood in mice Under conditions of the "forced swimming" test.

Materials and methods. The study was performed on outbred male mice. Exhausting physical activity was modeled in the "forced swimming" test in various aversive environments. The oxygen consumption by the muscle tissue, as well as the oxygen capacity of the blood, were estimated using the respirometry method (AKPM1-01L ("Alfa Bassens", Russia)).

Results. In the course of the study it was found out that in the group of the animals swimming in hot water (at the temperature of 41°C) as an aversive environment, there was no significant change in the oxygen consumption by mitochondria of striated muscle and by red blood cells in comparison with the intact group of the animals. At the same time, in the group of the mice, where cold water (at the temperature of 15°C) as an aversive environment was used, a statistically significant (by the end of the experiment) decrease in the swimming time was observed in relation to the intact group of the animals. It was accompanied by a decrease in the oxygen consumption by muscle mitochondria, with a constant level of the blood oxygenation. Under conditions of exhausting physical exertion, in the group of the animals that received Metaprot®, an increase in working capacity was noted in both hot and cold water. After peak days of working capacity, a slight decrease in physical activity was observed in both experimental groups. At the same time, it should be noted that oxygenation of blood and muscle tissue against the background of exhausting physical exertion in the group that received Metaprot®, did not differ from the group of intact animals in various aversive environments.

Conclusion. Thus, based on the obtained data, it can be assumed that under conditions of "forced swimming" with loading, the most profound changes in the structure and functions of the striated muscles are observed in animals in cold (15°C) water That is reflected in a decrease in the physical strain and in reducing the oxygen consumption by muscle tissue. The use of the drug Metaprot® promoted correcting the changes in the physical performance of the animals, which was reflected in its increase by 144.8% ($p < 0.05$), compared with the initial swimming time of this group, without the oxygen consumption by erythrocytes and mitochondria of striated muscles.

Keywords: exhausting physical overload, forced swimming with loading, oxygen consumption, blood oxygen capacity, respirometry, Metaprot®

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ВЛИЯНИЕ РАЗЛИЧНОЙ АВЕРСИВНОЙ СРЕДЫ НА ПОТРЕБЛЕНИЕ КИСЛОРОДА В МЫШЦАХ И КРОВИ У МЫШЕЙ В УСЛОВИЯХ ТЕСТА «ПРИНУДИТЕЛЬНОГО ПЛАВАНИЯ»

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Цель исследования – оценить влияние различной аверсивной среды на потребление кислорода в мышцах и крови у мышей в условиях теста «Принудительного плавания».

Материалы и методы. Исследование было выполнено на беспородных мышах-самцах. Истощающие физические нагрузки моделировали в тесте «Принудительного плавания» в различных аверсивных средах. Потребление кислорода мышечной тканью, а также кислородную емкость крови оценивали с помощью метода респирометрии (АКПМ1-01Л (Альфа Бассенс, Россия)).

Результаты. В ходе проведенного экспериментального исследования было установлено, что в группе животных, у которых в качестве аверсивной среды использовалась горячая вода (температура 41°С) существенного отличия потребления кислорода митохондриями поперечно-полосатой мускулатуры и эритроцитами в сравнении с интактной группой животных отмечено не было. В тоже время у группы мышей, где в качестве аверсивной среды использовали холодную воду (температура 15°С) продолжительность плавания (к концу эксперимента) была статистически ниже по отношению к интактной группе животных, сопровождаемое уменьшением потребления кислорода митохондриями мышц, при неизменном уровне оксигенации крови. В условиях истощающих физических нагрузок, в группе животных, получавшая Метапрот®, было отмечено нарастание работоспособности, как в горячей, так и в холодной воде. После пиковых дней работоспособности, в обеих экспериментальных группах наблюдалось незначительное падение физической активности. При этом, необходимо отметить, что оксигенация крови и мышечной ткани на фоне истощающих нагрузок в группе, получавшей Метапрот®, не отличалась от группы интактных животных в различных аверсивных средах.

Заключение. Таким образом, на основании полученных данных можно предположить, что в условиях принудительного плавания с отягощением у животных наиболее глубокие изменения функций поперечно-полосатой мускулатуры отмечаются в холодной воде (15°С), выступающей в роли стрессора, что отражается в снижении физической работоспособности, а также в снижении потребления кислорода мышечной тканью. Применение препарата Метапрот® способствовало корректировке возникших изменений физической работоспособности животных, что нашло свое отражение в ее повышении на 144,8% ($p<0,05$), в сравнении с исходным временем плавания данной группы, без изменения потребления кислорода эритроцитами и митохондриями поперечно-полосатых мышц.

Ключевые слова: истощающие физические нагрузки, потребление кислорода, кислородная емкость крови, респирометрия, Метапрот®

INTRODUCTION

Currently, a large number of people are exposed to exhausting physical overload. This category includes highly skilled athletes [1], as well as individuals whose professional activity is associated with a number of negative environmental factors affecting the body [2–4]. These include: reduced partial pressure of O_2 and CO_2, high and low temperatures, dustiness, desynchronosis leading to a breakdown of the adaptive capabilities of a person and the development of disadaptation [5].

It is worth noting that the influence of an aversive environment on the body under conditions of exhausting physical overload is realized through changes in the activity of skeletal muscles, while the main compensatory mechanisms in muscle tissue, in response to the stressor, are: increased oxygen consumption, activation of protein-synthetic processes, intensification of metabolic reactions, etc. [6, 7].

Thus, the assessment of changes in oxygen consumption by muscles and blood in various aversive environments can become the main strategy for developing means of preventing muscle fatigue.

MATERIALS AND METHODS

Laboratory work

The experimental study was performed on 80 outbred male mice weighing 23–25 g, obtained from the laboratory animal's nursery «Rappolovo» (St. Petersburg), and kept in the vivarium of Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. All reproducible manipulations

with animals complied with the rules of the «European Convention for the Protection of Vertebrate Animals» (Strasbourg, 1986). The mice were kept in the natural lighting mode of the vivarium; the air temperature and moderate humidity were 22–24°C and 60 ± 5%, respectively. The animals were kept in macrolone boxes with sawdust with free access to feed and water.

Initially, all the male mice were randomized by swimming time, and distributed into the following experimental groups: an intact group of mice underwent swimming with rest days (IN_c, the water temperature of 15° C) (n = 30), a negative control group (NC_c, the water temperature of 15°C) (n = 10) [8]; an intact group (IN_h, the water temperature of 41° C) (n = 30) and a negative control group (NC_h, the water temperature of 41°C) (n = 10) [9]. Two groups of mice (10 animals in each) were treated by «Metaprot» at the dosage of 25 mg/kg («Pharmproekt», Russia) [10].

Muscular Dysfunction Model

Validation method**s** for assessing the physical stress of the animals in an aversive environment (15°C) with a load of 20% of the body weight of the animal has already been carried out before [8]. Along with this method**s**, it could be of interest to assess physical performance in hot water [9]. On the 10th day of the experiment, the animals were decapitated with biological material collected. It was followed by an assessment of oxygen consumption by striated muscles and blood in various aversive environments.

Biomaterial sample preparation

In the work, skeletal muscles and blood were used as biological materials. The skeletal muscles were homogenized in Potter mechanical homogenizer with the addition of HEPES buffer. The obtained cell population was subjected to differential centrifugation: first in the mode of 3,500g for 5 min, then the supernatant was transferred to other tubes, and centrifugation was repeated in the second mode: 13000 g for 10 min. For the further analysis, the supernatant liquid was selected [11].

Respirometric analysis

Oxygen consumption in cell cultures was performed using AKPM1-01L laboratory respirometer (“Alfa Bassens”, Russia). The course of work was fully consistent with the manufacturer’s instructions attached to the device.

Methods of statistical analisys

Statistical processing was performed using the program “STATISTICA 6.0”. Intergroup differences were analyzed by parametric or non-parametric methods, depending on the type of distribution. T-Students test was used as a parametric criterion; Mann-Whitney U-test was used for a nonparametric one. The differences were considered significant at $p < 0.05$.

RESULTS

As a result of the conducted experimental study in various aversive environments, it was noted that in the group of the intact animals, the duration of swimming was unchanged throughout all the days of the experiment (Fig. 1).

The swimming time of the initial day of the experiment (the 1st day) in the group of NC_c mice was 128.7±9.5 seconds. Then, starting from the second day of the experiment, the duration of swimming of animals increased linearly, while the peak of physical performance was noted on the fifth day of swimming of mice with loading (161.3±11.0 sec.). On the peak day, the duration of swimming was longer by 25.3% ($p < 0.05$) relative to the initial day of swimming in this group. However, from the sixth day of the experiment in the group of the mice subjected to daily physical overload, there was a slight decrease in their swimming time, which was shorter in comparison with the day of maximum swimming time of this group by 23.1% ($p < 0.05$). It should be pointed out that the tendency to a noticeable decrease in swimming was noted beginning with the 7th day and until the end of the experiment (Fig. 1). The performance of mice in the “forced swimming” test with loading in the NC_c group was lower by 51.4% ($p < 0.05$) relative to the initial swimming of the animals in this group and by 56% ($p < 0.05$) in comparison with the initial time of the performance in the IN_c. group.

Against the background of the daily administration of Metaprot® to the mice, a linear increase in their performance was noted. The day of maximal swimming of the animals was recorded on the 7th experimental day. It was higher relative to the baseline data of this group by 144.8% ($p < 0.05$) and 140.3% ($p < 0.05$) and 165.1% ($p<0.05$) relative to the intact and negative control groups. Subsequently, a slight smooth drop in working capacity was observed, while on the 10th experimental day, the swimming time of the animals was longer than that of the intact group and the negative control group by 54.7% ($p < 0.05$) and 251.5% ($p < 0.05$), respectively.

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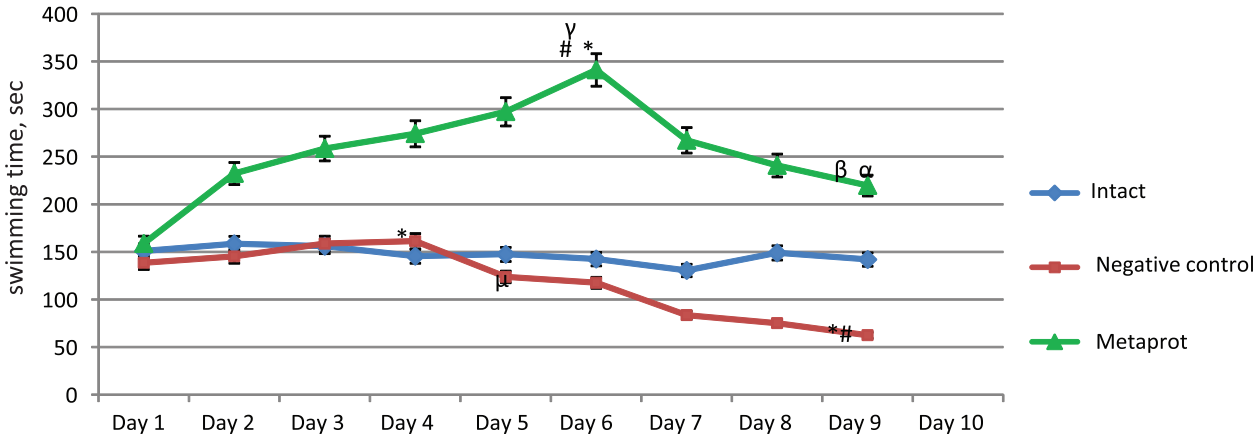

Figure 1 - Duration of mice's swimming time in the test "forced swimming with a load" in cold water

*Note: * – statistically significant relative to the initial swimming time of this group (Student's t-test, (p <0.05)); μ – statistically significant relative to the peak day of swimming for this group (Student's t-test, (p <0.05)); # – statistically significant relative to the initial swimming time of the animals' intact group of (Student's t-test, (p <0.05)); γ – statistically significant relative to the initial swimming time of the animals' negative control group (Student's t-test, (p <0.05)); в – statistically significant relative to the final swimming time of the animals' negative control group of (Student's t-test, (p <0.05)); α – statistically significant relative to the end swimming time of an intact group of animals (Student's t-test, (p <0.05)).*

When estimating forced swimming of the mice in hot water, a linear increase in the performance of animals was noted. Thus, the highest working capaity was noted on the 4th day of the experiment. It was higher by 73% (p<0.05) in comparison with the initial swimming time and by 140.7% (p <0.05) in comparison with the initial swimming day of the group of intact animals (Fig. 2). Starting from the 4th experimental day, the performance of the animals began to decline significantly. So, on the 7th day of the experiment, the swimming time of the mice was shorter by 56.4% (p <0.05) compared to the peak day of the mice's working capacity in the negative control group and shorter by 33.5% (p <0.05) in comparison with the IN_h group of the animals. It should be noted that by the 10th experimental day, the working capacity of the animals subjected to daily physical overload in hot water had got lower by 2.8 times (p <0.05) in comparison with the initial data of this group. Besides, in comparison with the swimming time of the IN_h group, the mice's working capacity of the negative control group was 2.0 times lower (p<0.05) because of hot water.

Under conditions of exhausting physical overload in the group of the mice treated with Metaprot®, an increase in their working capacity from the 1st to the 6th experimental days (the reak of swimming) was observed. It was found out that the peak of physical performance was higher by 129.2% (p<0.05), relative to the initial swimming time of the group receiving Metaprot®. It should be noted that the duration of swimming on the peak day in the group that received Metaprot® was longer compared to the intact and negative control groups, by 193% (p<0.05) and 110.6% (p<0.05), respectively. It is worth noting that by the end of the experiment there had not been sharp drops in efficiency. The duration of swimming of the mice treated with Metaprot®, on the final experimental day was higher by 119% (p<0.05) and 330.2% (p<0.05), relative to the 10th day of the intact and negative control groups.

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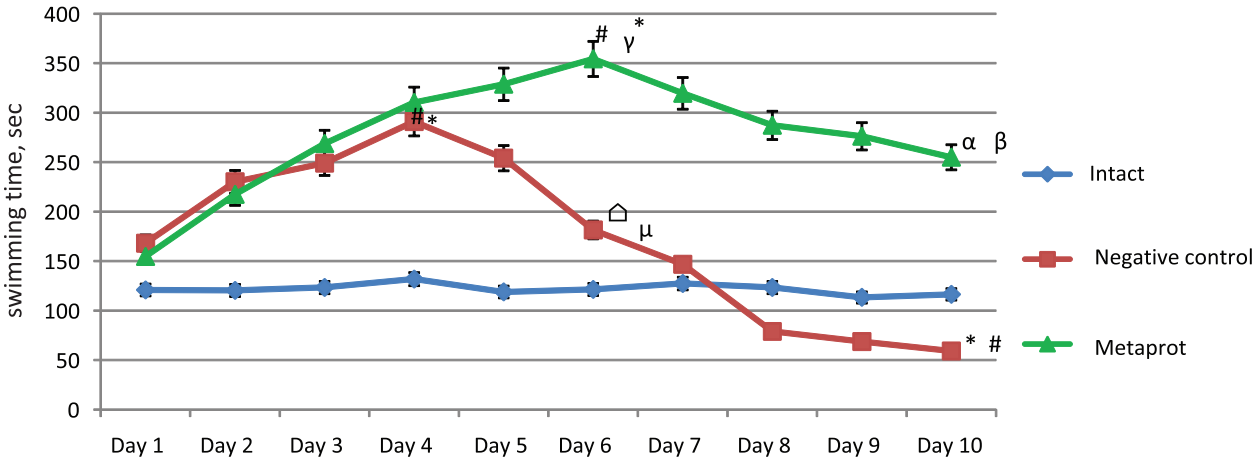

Figure 2 – Duration of mice's swimming time in the "Forced swimming test with loading" in hot water

*Note: * – statistically significant relative to the initial swimming time of this group (Student's t-test, (p <0.05)); # – statistically significant relative to the initial swimming time of the animals' intact group (Student's t-test, (p <0.05)); μ – statistically significant relative to the peak day of swimming for this group (Student's t-test, (p <0.05)); ⌂ – statistically significant relative to the peak day of swimming of the animals' intact group (Student's t-test, (p <0.05)); γ – statistically significant relative to the initial swimming time of the animals' negative control group (Student's t-test, (p <0.05)); β – statistically significant relative to the final swimming time of the animals' negative control group (Student's t-test, (p <0.05)); α – statistically significant relative to the final swimming time of the animals' intact group (Student's t-test, (p <0.05))*

As Fig. 3 shows, in the *animals' negative control* group, the oxygen consumption by erythrocytes compared to the intact group, was not statistically and significantly different in hot water.

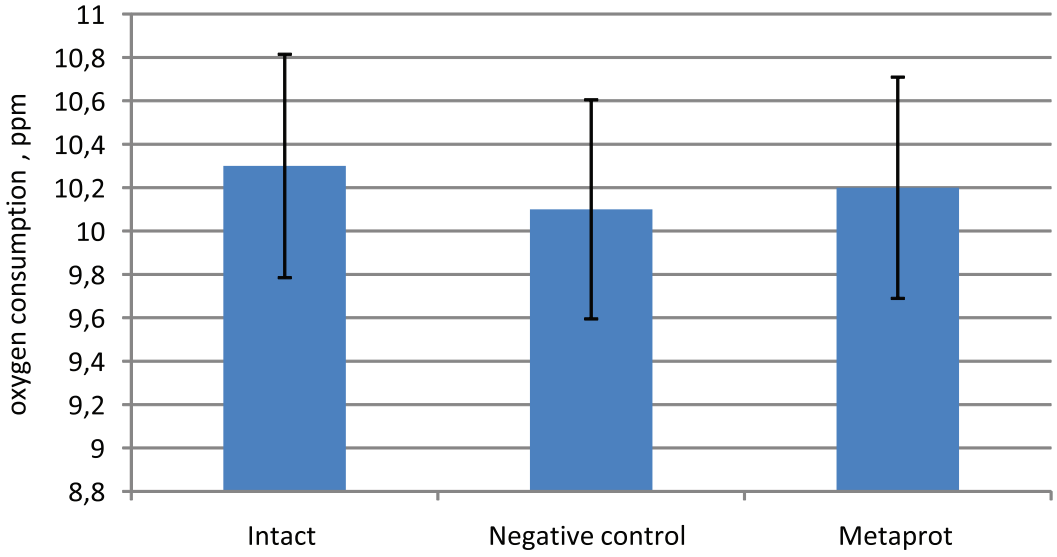

Figure 3 – Estimation of oxygen consumption by red blood cells against the background of the "forced swimming test with loading" in hot water

In the group of the intact animals and rats receiving Metaprot®, no changes in blood oxygenation were detected.

While the oxygen consumption by mitochondria of striated muscles in the animals' negative control group was 1.8 times lower (p <0.05) in comparison with the IN_h group of mice,there were no changes established in the oxygen consumption by the muscles in the group that received Metaprot®, relative to the animals' intact group. However, relative to the negative control group, this parameter was higher by 2.6 times (p<0.05).

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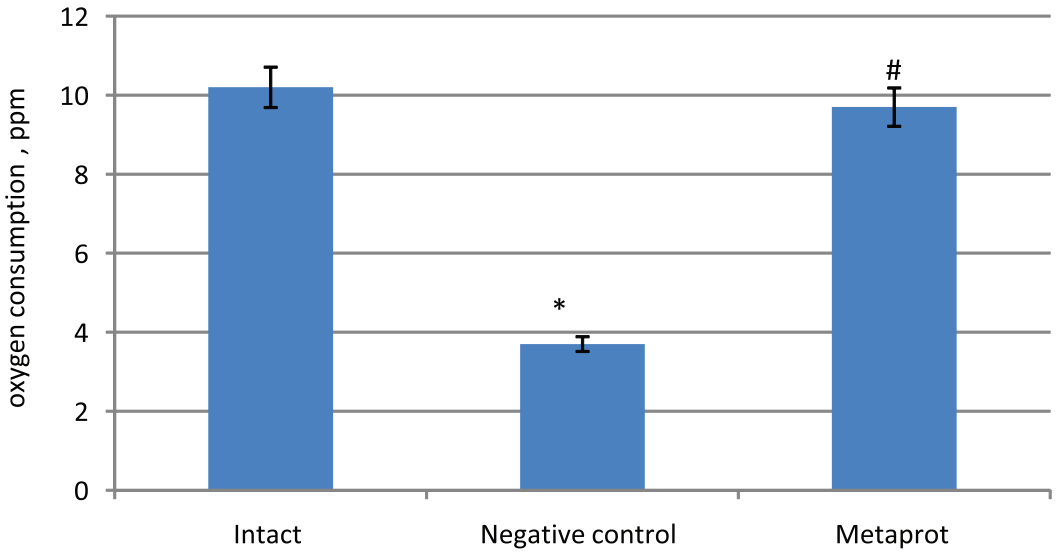

Figure 4 – Evaluation of the oxygen consumption by mitochondria of striated muscles against the background of the "forced swimming test with loading" in hot water

*Note: * – statistically significant relative to the animals' intact group (Student's t-test, (p <0.05)); # – statistically significant relative to the animals' negative control group (Student's t-test, (p <0.05))*

In the group of negative control mice, where cold water was used as an aversive environment, there was a statistically significant decrease in the oxygen consumption by muscle mitochondria by 2.4 times (p<0.05), relative to the intact group of the animals (Fig. 5, 6). Hereby, the blood oxygenation level remained unaffected.

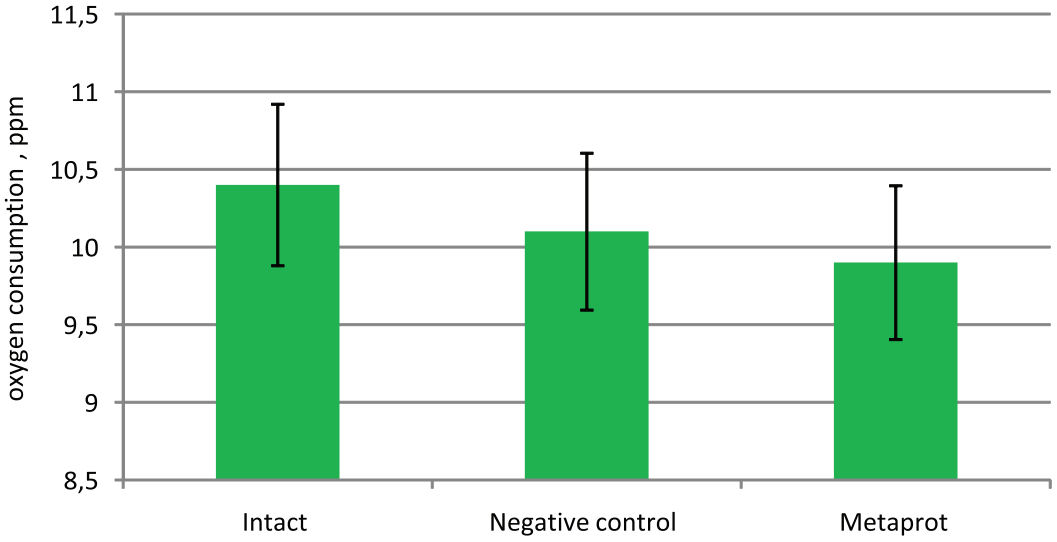

Figure 5 – Evaluation of oxygen consumption by red blood cells against the background of the "forced swimming test with loading" in cold water

It should be noted that the oxygen consumption by the mitochondria of the striated muscles in the group that received Metaprot® was higher, compared to the group of the animals of the negative control, by 4.3 times (p<0.05). As for the comparison with the group of intact animals, there were no statistically significant changes detected. It was also noted that against the background of "forced swimming" in cold water, in the group of the mice that received Metaprot® as the reference drug,, their blood oxygenation level remained unaffected.

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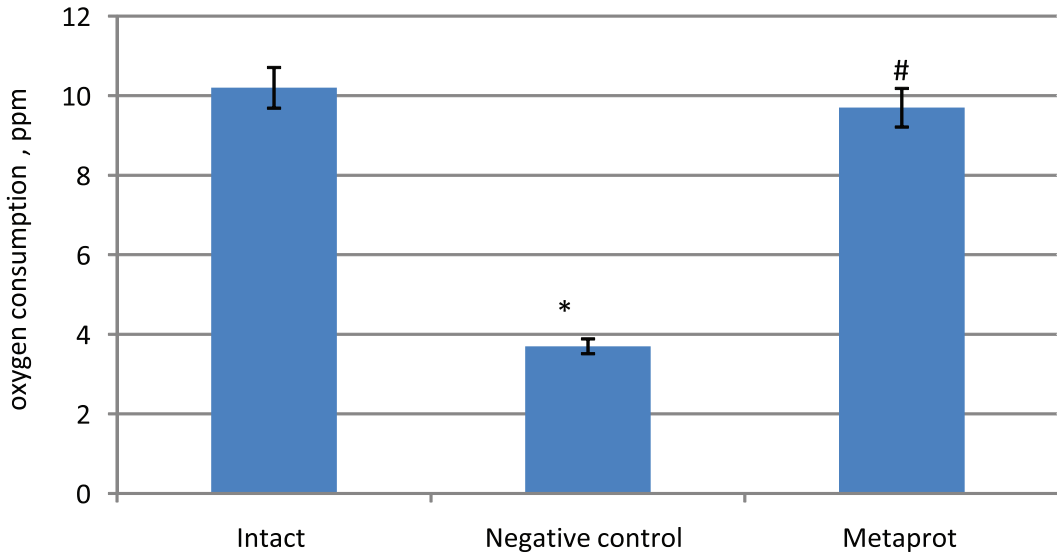

Figure 6 – Estimation of oxygen consumption by mitochondria of striated muscles against the background of the "forced swimming test with loading" in cold water

*Note: * – statistically significant relative to the animals' intact group (Student's t-test, (p <0.05)); # – statistically significant relative to the animals' negative control group (Student's t-test, (p<0.05)).*

DISCUSSION

The optimal level of physical activity is one of the main components of a healthy lifestyle, providing the necessary quality of life of the population [12]. It has been found out that individuals suffering from physical inactivity have an increased risk of developing diabetes, hypertension, cancer, obesity, and mental disorders (anxiety, panic attacks, depression, cognitive deficiency) [13]. However, excessive, depleting physical exertion, on the contrary, are a powerful stress factor and can contribute to a significant deterioration in the quality of life of the population, cause the development of cardiovascular pathology, and a decrease in the intensity of immune responses [14]. In many ways, the stress on the human body is determined by the nature of the unfavorable (aversive) environment, which aggravates the effect of the stressor on the body [15]. Under conditions of depleting physical overload, the effect of an aversive environment on the body is largely realized through a change in the activity of skeletal muscles – the main component of optimal physical activity [7]. Hereby, in response to the action of an unfavorable environmental factor the main compensatory mechanisms in the muscle tissue are: increased oxygen consumption, activation protein-synthetic processes, the intensification of metabolic reactions and the activation of metabotropic transport systems [6]. However, with progressive muscle fatigue, these compensatory mechanisms "turn off", and an increase in the oxygen consumption by tissues is not accompanied by an increase in the energy output, which, in turn, reduces the activity of striated muscles and the overall level of physical performance [16].

In the carried out study on the impact of the nature of an aversive environment on the level of oxygen consumption in muscle tissue and blood oxygen capacity, it was found out that in the animals' negative control group, in which hot water (the temperature of 41^0C) was used as an aversive environment, a change in the working capacity was observed: in mice, the peak of swimming was the 4^{th} day – 70% ($p<0.05$), relative to the initial day of swimming in this group. A similar pattern of change in physical activity in the mice's negative control group can be presumably mediated by the action of the aversive environment (hot water) on the skeletal muscle activity of the experimental animals. Under current conditions (hot water), dilatation of blood vessels of striated muscles is likely to be noted, which, despite the increased muscle need for oxygen, increases the delivery of oxygen and nutrients to skeletal muscle myocytes [17]. In addition, in the literature data it is reported that thermal effects on skeletal muscles activate metabolic processes and prevent muscle fatigue [17, 18]. In the future, a decrease in the level of performance was observed, which was lower by 2.8 times ($p<0.05$) and 2.0 times ($p<0.05$) relative to the initial swimming time value of the negative control group of mice, and the intact group, respectively. There were changes in the oxygen consumption only by the mitochondria of the striated muscles. It was lower by 1.8 times ($p<0.05$) in comparison with the intact group of animals. This fact of impairment can probably be attributed to the fact that an unfavorable environment (hot water) can lead to structural changes in the muscles, namely, the unfolding and denaturation of the protein, which, in turn, can contribute to the violation of the contractile function of the muscles [19].

At the same time, a group of mice (negative control),

ОРИГИНАЛЬНАЯ СТАТЬЯ
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where cold water (the temperature of 15°C), was statistically significant (by the end of the experiment) relative to the intact group of animals, the decrease in swimming duration, accompanied by a decrease in the oxygen consumption by muscle mitochondria, with a constant level of blood oxygenation. At the same time, on the 5th day of the experiment, the duration of swimming of mice in cold water increased by 25.3% ($p<0.05$) relative to the intact group. The results may be associated with the peculiarities of the effect of low temperatures on the body. Thus, *Naresh C., et al., 2017,* showed that the effect of low temperatures on muscle tissue causes significant metabolic changes in muscles, followed by activation of the mitochondrial uncoupling protein,Type 1 (UCP-1) [20]. Activation of UCP-1 in striated myocytes helps to reduce the proton gradient in the mitochondrial matrix, which, in turn, leads to the intensification of glycolysis with reduced ATP production, accompanied by increased thermogenesis. That can contribute to the preservation of muscle activity and, consequently, physical performance [21]. However, this compensatory mechanism has a short-term effect**.** Later, a significant decrease in physical activity was noted (a decrease in the duration of swimming of mice in cold water in comparison with the intact group of animals by 105.9% ($p<0.05$) by the 10th day of the experiment). However, later, with sufficient oxygenation of the blood (in cold water in mice, no decrease in the oxygen transport function of the blood was observed), hyperfunction of the UCP-1 protein contributes to the separation of oxidation and phosphorylation due to the practical loss of the proton gradient of the mitochondrial matrix [22]. That leads to a decrease in the oxygen utilization by skeletal muscles and, as a result, the synthesis of macroergic compounds deteriorates, the activation of oxidative stress takes place, which negatively affects the level of physical activity [23].

It can be assumed, that in addition to the activation of thermogenin UCP-1 under conditions of the effect of cold temperatures on the muscle tissue, there is a dysfunction of metabotropic transport systems GLUT4 [24]. The activity of AMP-activated kinase also decreases [25], which impairs the entry of cross-striped muscle glucose into myocytes and aggravates energy shortages.

Under conditions of exhaustive physical overload, in the group of the animals that received Metaprot®, an increase in their working capacity was noted, both in hot (from the 1st to the 6th experimental day (swimming peak) and in cold water - the maximum day of the animals' swimming was the 7th one. Further on, in both experimental groups there was a slight smooth drop in performance. At the same time, it should be noted, that the oxygenation of the blood and the muscle tissue against the background of debilitating loads in the group receiving Metaprot® remained unchanged in comparison with the group of intact animals in various aversive environments. An increase in the physical performance of the animals against the background of Metaprot® can probably be attributed to the inhibition of glycogen disintegration, a decrease in heat production, and also the activation of the synthesis of mitochondrial proteins (gluconeogenesis enzymes) [26, 27].

CONCLUSION

Thus, based on the obtained data, it can be assumed that under conditions of forced swimming with loading in animals, the most profound changes in the structure and functions of the striated muscles are observed in cold water (15^0C) acting as a stressor. That is reflected in a decrease in physical performance and in reducing the oxygen consumption by the muscle tissue. The use of the drug Metaprot® helped to correct the changes in the physical performance of the animals, which was reflected in its increase by 144.8% ($p<0.05$) compared to the initial swimming time of this group, without an increase of the oxygen consumption by red blood cells and mitochondria of striated muscles.

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CONFLICTS OF INTEREST

The authors and peer reviewers of this paper report no conflicts of interest.

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