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EVALUATION OF THE MITOCHONDRIA RESPIROMETRIC FUNCTION IN THE CONDITIONS OF PATHOLOGIES OF VARIOUS GENESES

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The aim *of the paper is to assess the change in the mitochondrial respirometric function under conditions of various pathologies.* ***Materials and methods.*** *The study was performed on male Wistar rats. Experimental focal cerebral ischemia, traumatic brain injury, coronary occlusive myocardial infarction and muscle dysfunction were used as pathological models. Focal ischemia was reproduced by the method of irreversible thermocoagulation of the middle cerebral artery. Traumatic brain injury was modeled by the method of free fall of the load. Experimental myocardial infarction was reproduced by ligating the descending branch of the left coronary artery. Muscle dysfunction was modeled by the method of «forced swimming with a 20% burden». The respiratory function of mitochondria was assessed by the method of respirometry by the change in oxygen consumption when introducing mitochondrial respiration into the medium: Oligomycin, Rotenone and FCCP. Additionally, we evaluated the intensity of the glycolysis process and the activity of respiratory complexes I, II, IV and V. In order to comprehensively assess the respiratory function, an ELISA study was conducted to determine the concentration of ATP, mitochondrial ATP synthetase, cytochrome C oxidase and NADP-Oxidase 4.* ***Results.*** *In the course of the study it was established that under conditions of experimental cerebral ischemia, traumatic brain injury, myocardial infarction and muscle dysfunction, the ATP-generating ability of mitochondria the maximum breathing and respiratory capacity deteriorated, herby the decrease in overall respiratory function was accompanied by an increase in glycolysis, which was uncompensated, as well as dysfunction of mitochondrial complexes I, II, IV and V, confirmed by an increase in NADPH oxidase 4 activity and a decrease in cytochrome C oxidases and ATP synthetase. As a result, the observed changes in mitochondrial respiration function contributed to a decrease in ATP concentration under conditions of cerebral ischemia - by 3.2 times ($p < 0.05$), traumatic brain injury – by 2.6 times ($p < 0.05$), myocardial infarction – by 1.8 times ($p < 0.05$) and muscle dysfunction – by 4 times ($p < 0.05$).* ***Conclusion.*** *Basing on the data obtained, we can assume that in conditions of cerebral ischemia, traumatic brain injury, myocardial infarction and muscle dysfunction, there is deterioration of the mitochondrial respirometric function with inhibition of ATP synthesis and increased glycolysis.*

Keywords: *cerebral ischemia, myocardial infarction, traumatic brain injury, muscle dysfunction, respirometry*

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ОЦЕНКА РЕСПИРОМЕТРИЧЕСКОЙ ФУНКЦИИ МИТОХОНДРИЙ В УСЛОВИЯХ ПАТОЛОГИЙ РАЗЛИЧНОГО ГЕНЕЗА

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Цель исследования – *оценить изменение респирометрической функции митохондрий в условиях различных патологий.* ***Материалы и методы.*** *Исследование выполнено на крысах самцах линии Wistar. В качестве модельных патологий в работе использовали экспериментальную фокальную ишемию головного мозга, черепно-мозговую травму, коронарооккклюзионный инфаркт миокарда и мышечную дисфункцию. Фокальную ишемию воспроизводили методом необратимой термокоагуляции средней мозговой артерии. Черепно-мозговую травму моделировали методом свободного падения груза. Экспериментальный инфаркт миокарда воспроизводили лигированием нисходящей ветви левой коронарной артерии. Мышечную дисфункцию моделировали методом «принудительного плавания с 20% отягощением». Дыхательную функцию митохондрий оценивали методом респирометрии по изменению потребления кислорода при внесении в среду разобщителей митохондриального дыхания: олигомицин, ротенон и FCCP. Дополнительно оценивали интенсивность процесса гликолиза и активность дыхательных комплексов I, II, IV и V. С целью комплексной оценки респирометрической функции проводили ИФА-исследование с определением концентрации АТФ, митохондриальной АТФ-синтетазы, цитохром-с-оксидазы и НАДФ-оксидазы 4.* ***Результаты.*** *В ходе проведения исследования установлено, что в условиях экспериментальной ишемии головного мозга, черепно-мозговой травмы, инфаркта миокарда и мышечной дисфункции отмечено ухудшение АТФ-генерирующей способности митохондрий, максимального уровня дыхания и респираторной емкости, при этом снижение общей респирометрической функции сопровождалось усилением процессов гликолиза, которое носило некомпенсированный характер, а также дисфункцией митохондриальных комплексов I, II, IV и V, подтверждаемой увеличением активности НАДФ-оксидазы 4 и снижением активности цитохром-с-оксидазы и АТФ-синтетазы. В итоге наблюдаемые изменения респирометрической функции митохондрий способствовали уменьшению концентрации АТФ в условиях церебральной ишемии – в 3,2 раза ($p<0,05$), черепно-мозговой травмы – в 2,6 раза ($p<0,05$), инфаркта миокарда – в 1,8 раза ($p<0,05$) и мышечной дисфункции – в 4 раза ($p<0,05$).* ***Заключение.*** *Основываясь на полученных данных можно предположить, что в условиях ишемии головного мозга, черепно-мозговой травмы, инфаркта миокарда и мышечной дисфункции наблюдается ухудшение респирометрической функции митохондрий с угнетением синтеза АТФ и усилением процессов гликолиза.*

Ключевые слова: *ишемия головного мозга, инфаркт миокарда, черепно-мозговая травма, мышечная дисфункция, респирометрия митохондрий*

INTRODUCTION

Mitochondria are cellular organelles, the main sources of energy in the cell, which also play a significant role in regulating the processes of caspase-dependent and caspase-independent pathways of apoptosis and redox signaling of the cell [1]. In accordance with this, three leading mitochondrial functions are distinguished: respirometric, i.e. ensuring the synthesis of macroergs in the process of redox reactions in the electron-transport mitochondrial respiratory chain [2]; apoptosis-regulating, i.e. regulation of the initiation and progression of the apototic signal [3] and antioxidant, i.e. inactivation of free radicals [4]. At the same time, the main function of mitochondria is respirometric, which provides the relationship between the redox state of the cell and the activation of proapoptotic molecules [5]. Currently, it has been established that the number of "mitochondrial diseases", the pathogenesis of which is associated with impaired functional activity of mitochondria, comprises ischemic stroke, Alzheimer's disease, traumatic brain injury, ischemic heart disease and myocardial infarction, muscle fatigue [6]. In the scientific literature it is reported that in the pathogenesis of these diseases, one of the central roles is assigned to the energy deficit that occurs when there is mitochondrial dysfunction [7]. At the same time, the reduction in the formation of

macroergic compounds is inseparably linked with the disruption of electron transport in the respiratory chain of mitochondria and the dissociation of the reactions of subcomplexes I, II, IV and V, which leads to the activation of glycolysis and a significant decrease in ATP synthesis [8]. In addition, dysfunction of complexes I and II contributes to the redistribution of oxygen flow towards the formation of prooxidants, in particular the superoxide radical [9] and a decrease in the formation of ATP leads to the activation of the caspase-dependent pathway of apoptosis [10]. At the same time, the intensification of anaerobic oxidation processes leads to the accumulation of non-oxidized products of metabolism. That shifts the intracellular pH value in the acidic direction. Under current conditions, activation of pro-apoptotic signaling molecules (proteins of the Bid / Bax family) is noted, triggering a caspase-independent pathway of apoptosis, which enhances cellular destruction [11]. Thus, the assessment of the change in mitochondrial respiration function under conditions of various pathologies may be the basis for the development of mitochondrial disease treatment strategies, which can eliminate energy deficit and associated apoptosis and oxidative modification of cellular structures.

MATERIALS AND METHODS

Biological model

The study was performed on 50 male Wistar rats weighing 220–240 grams, obtained from the nursery of laboratory animals "Rappolovo". The contents and all animal manipulations complied with the requirements of the European Convention for the Protection of Vertebrate Animals used for experiments and other scientific purposes (Strasbourg, 1986). The rats were housed in macrolon cages, where granulated wood faraction was used as litter at the relative humidity of 60 ± 5% and the air temperature of 22 ± 20°C. The feed and water were received by the animals in the free access. During the study, the following experimental groups were formed: intact animals (n = 10), the rats with reproduced cerebral ischemia (n = 10), TBI (n = 10), myocardial infarction (n = 10) and muscle dysfunction (n = 10).

Model of focal cerebral ischemia

Focal cerebral ischemia was modeled by irreversible right-sided thermocoagulation of the middle cerebral artery under chloral hydrate anesthesia (350 mg / kg). The area below and to the right of the eye was depilated, an incision was made. The soft tissues were moved apart, exposing the process of the zygomatic bone, which was removed. Then a trephine opening was burred and the middle cerebral artery was burned through by a thermocoagulator under its intersection with the olfactory tract. Later on , the topography of soft tissues was restored as far as possible. The suture was treated with a 5% iodine solution [12]. The biomaterial was sampled on the 4th day after the reproduction of focal ischemia.

Model of experimental traumatic brain injury

Traumatic brain injury was modeled by the method of a free fall of load of 150 g from a height of 50 cm to the parietal region of the brain of rats. The animals were placed in a special installation, which is a hollow cylinder with backing and retainers, in which the head of rats was fixed. After hat the load was released [13]. The biomaterial was sampled on the 4th day after the reproduction of the TBI.

Muscle Dysfunction Model

Muscle dysfunction was reproduced by the method of "forced swimming with 20% weight" after determining the initial value of the swimming time, the animals were subjected to training tests for 28 days (the swimming time was 20% of the initial index). On days 7, 14, 21, and 28, the rats were subjected to the exhausting test — swimming until they completely abandoned the struggle for life, after which the animals were taken out of from the water. The biomaterial was taken on day 28 [14].

Model of acute myocardial infarction

In animals under conditions of chloral hydrate anesthesia (350 mg / kg) and artificial ventilation of the lungs, the skin on the previously depilated area was cut in the sternum area and the muscles were dissected. Next, the IV rib was isolated, and the chest was opened. The myocardium was separated from the epicardium and the heart was led into the wound. Subsequently, the ligation of the descending branch of the left coronary artery with silk thread was carried out. The wound was sutured in layers. The biomaterial was taken 24 hours after the operation [15].

Biomaterial sampling and sample preparation

Brain, myocardium and muscle tissue (*m.quadriceps femoris*) of the rats were used as biomaterial. The animals were decapitated under chloral hydrate anesthesia (350 mg/kg), their organs were harvested. After that the biomaterial was homogenized in a mechanical homogenizer in a selection medium (1 mmol EDTA, 215 mmol mannitol, 75 mmol sucrose, a 0.1% BSA solution, 20 mmol HEPES, with a pH of 7.2). The cell population was obtained by differential centrifugation, for which the obtained biogenic homogenate was centrifuged in the mode of 1.400 g → 3 min. at 40°C. After that the supernatant was transferred into 2 ml tubes. Next, the resulting supernatant was centrifuged at 13000 g → 10 min and the supernatant (the culture contains native mitochondria) was removed for analysis [16].

Respirometric analysis

The analysis of the state of the mitochondrial respiratory function was carried out by the method of respirometry using the AKPM1-01L laboratory respirometer system (Alfa Bassens, Russia). The mitochondrial respi-

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2019-7-1-20-31

ratory function was assessed by the change in the oxygen consumption in the medium against the introduction of mitochondrial respiratory uncouplers. The latest in the experiment were: Oligomycin 1 µg / ml; 4 – (trifluoromethoxy) phenyl) hydrazono) malononitrile (FCCP-1 µM); rotenone – 1 µM; sodium azide – 20 mmol. The oxidation substrates were: glucose – 15 mmol; pyruvic acid – 10 mmol; malate – 1 mmol; succinate – 10 mmol; ascorbate – 2 mmol; ADP – 1 mmol; N, N, N ‘, N’-tetramethyl-1,4-phenylenediamine (TMPD- 0.5 mmol). The overall assessment of mitochondrial function was determined by the level of oxygen consumption in the medium after sequential addition of oligomycin, FCCP and rotenone to the medium, and the ATP-generating ability was determined (by the difference in oxygen consumption after the addition of FCCP and oligomycin); the maximum level of respiration (according to the difference in oxygen consumption after the addition of FCCP and rotenone) and the respiratory capacity (according to the difference in oxygen consumption after the addition of FCCP and the basal level of oxygen consumption). The activity of glycolysis processes was evaluated when glucose was used as an oxidation substrate during the registration of oxygen consumption under the conditions of sequential addition of glucose, oligomycin and sodium azide to the medium. The intensity of glycolysis was determined according to the difference in oxygen consumption after adding glucose and the basal level of oxygen consumption; the intensity of glycolytic capacity was determined according to the difference in oxygen consumption after adding oligomycin and glucose; and the intensity of glycolytic reserve was determined according to the difference in oxygen consumption after adding glucose and sodium azide. Additionally, the activity of complexes I, II, IV, and V of the mitochondrial respiratory chain was evaluated. The activity of complex I was determined by the difference in oxygen consumption after adding the malate / pyruvate and rotenone mixture to the medium. The activity of complex II was evaluated by the difference in oxygen consumption after adding succinate and oligomycin to the medium. The activity of complex IV was determined by the difference in oxygen consumption after adding the mixture of rotenone / TMPD / ascorbate and sodium azide to the medium. The activity of complex V was evaluated by the difference in oxygen consumption after adding rotenone and ADP to the medium. During the analysis, the biosample volume was 275 µl, and 25 µl of injected analyzers. The oxygen consumption was determined in ppm [19].

ELISA – study

In this study, the concentration of ATP, mitochondrial ATP synthetase-(mATP), cytochrome C oxidase (CoX), and NADP oxidase 4 (NOX4) were determined by ELISA in the supernatants of the myocardial, brain and muscle tissues. We used species-specific sets of reagents produced by *Cloud clone corp.* (USA). The sample preparation and the course of the analysis corresponded to the instructions attached to the enlistment.

Statistical analysis methods

Statistical analisys of the obtained results was performed using the stat-analysis package STATISTICA 6.0. The data were presented as M ± SEM. The comparison of medium groups was performed using the ANOVA method with the post-test of Newman-Keuls at $p < 0.05$.

RESULTS

During the overall assessment of the mitochondrial respiratory function under conditions of various pathologies, it was found out that in rats with TBI and cerebral ischemia (Fig. 1), compared with the intact animals, there was a decrease in ATP-generating ability of mitochondria by 1.75 times ($p < 0, 05$) and by 4.6 times ($p < 0.05$), respectively. A decrease in the maximum level of respiration and respiratory capacity relative to intact rats was also noted in animals with cerebral ischemia by 2.85 times ($p < 0.05$) and by 2.13 times ($p < 0.05$), respectively. Against the background of the experimental traumatic brain injury, the animals compared to intact rats, showed a decrease in the maximum level of respiration by 1.77 times ($p < 0.05$) and respiratory capacity by 3.92 times ($p < 0.05$).

Under conditions of myocardial infarction (Fig. 2) in rats, there was a decrease in ATP-generating activity, the maximum level of respiration and respiratory capacity relative to the group of intact animals by 2.27 times ($p < 0.05$); by 2.98 times ($p < 0.05$) and by 2.78 times ($p < 0.05$), respectively.

In rats, against the background of muscle dysfunction (Fig. 3) compared with intact animals, a decrease in the maximum level of respiration, ATP-generating activity and respiratory capacity was observed by 3.28 times ($p < 0.05$); by 4.62 times ($p < 0.05$) and by 2.13 times ($p < 0.05$), respectively.

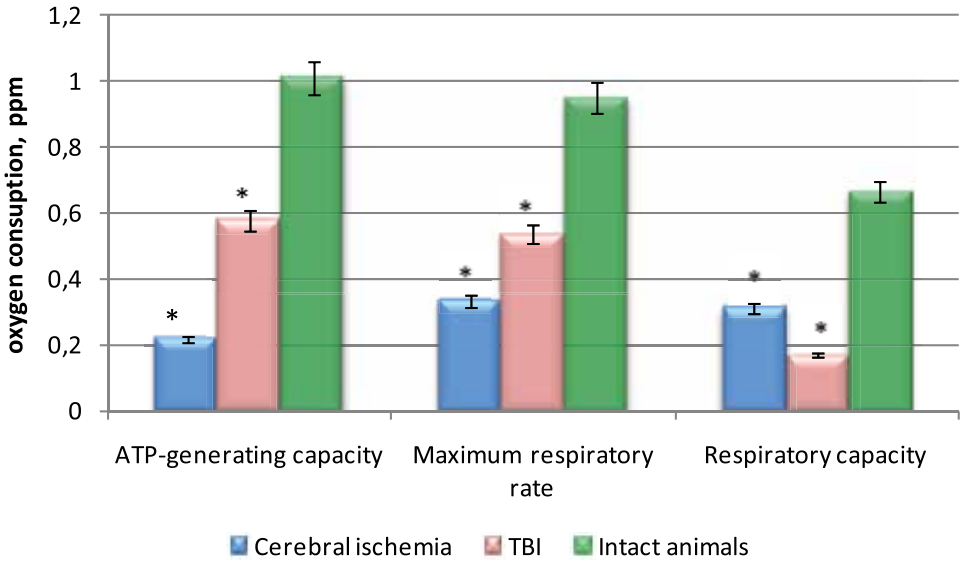

Figure 1. General assessment of mitochondrial respiration function under conditions of cerebral ischemia and traumatic brain injury

*Note: * – statistically significant relative to the group of intact animals (Newman-Keuls test, p <0.05)*

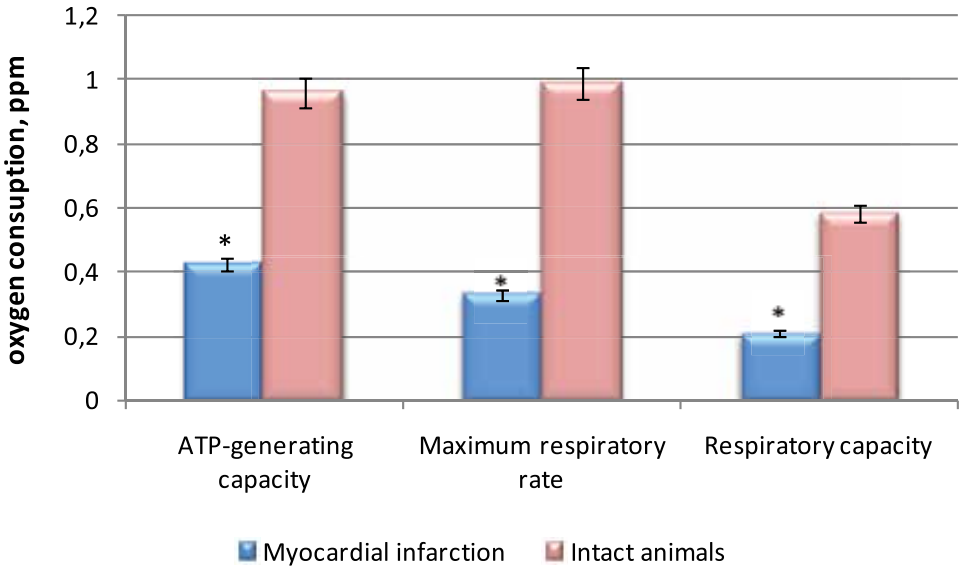

Figure 2. General assessment of the mitochondrial respiration function in experimental myocardial infarction

*Note: * – statistically significant relative to the group of intact animals (Newman-Keuls test, p <0.05)*

ОРИГИНАЛЬНАЯ СТАТЬЯ
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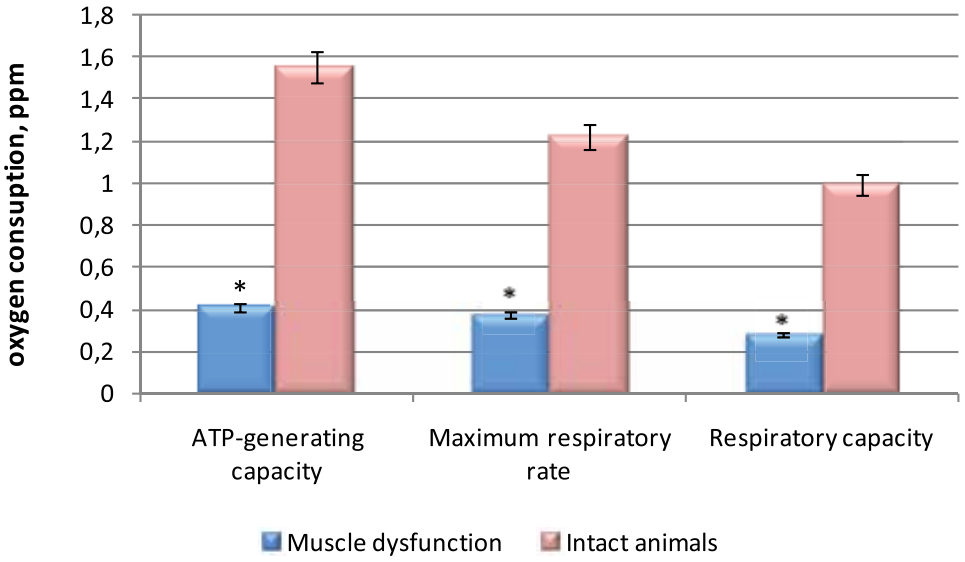

Figure 3. General assessment of mitochondrial respiration function under conditions of muscle dysfunction

*Note: * – statistically significant relative to the group of intact animals (Newman- Keuls test, p <0.05)*

When assessing glycolytic processes under conditions of various pathologies it was found out that in animals with TBI and cerebral ischemia (Fig. 4) there was an increase in glycolysis intensity compared to the group of intact animals by 18.04 times (p <0.05) and by 23.89 times (p <0.05), respectively. At the same time, in rats with experimentally reproduced cerebral ischemia, a decrease in glycolytic capacity relative to the group of intact animals was observed by 4 times (p<0.05), and the level of glycolytic reserve got a negative value (Fig. 2). Against the background of TBI in rats, in comparison with the intact group of animals, the glycolytic capacity and glycolytic reserve decreased by 22.6 times (p <0.05) and by 6 times (p <0.05), respectively.

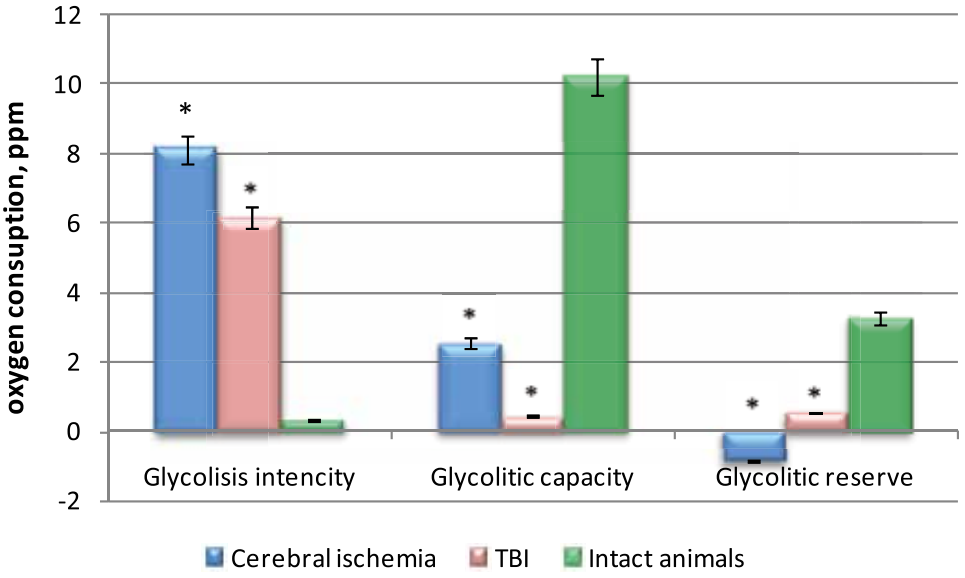

Figure 4. Assessment of changes of the glycolysis process in experimental cerebral ischemia and traumatic brain injury conditions

*Note: * – statistically significant relative to the group of intact animals (Newman- Keuls test, p <0.05)*

Under conditions of myocardial infarction in experimental animals (Fig. 5), the intensity of glycolysis processes exceeded that of the intact group of animals by 17.3 ($p < 0.05$) times, against the background of a decrease in glycolytic capacity and glycolytic reserve by 9.25 times ($p < 0.05$) and by 37.28 times ($p < 0.05$), respectively.

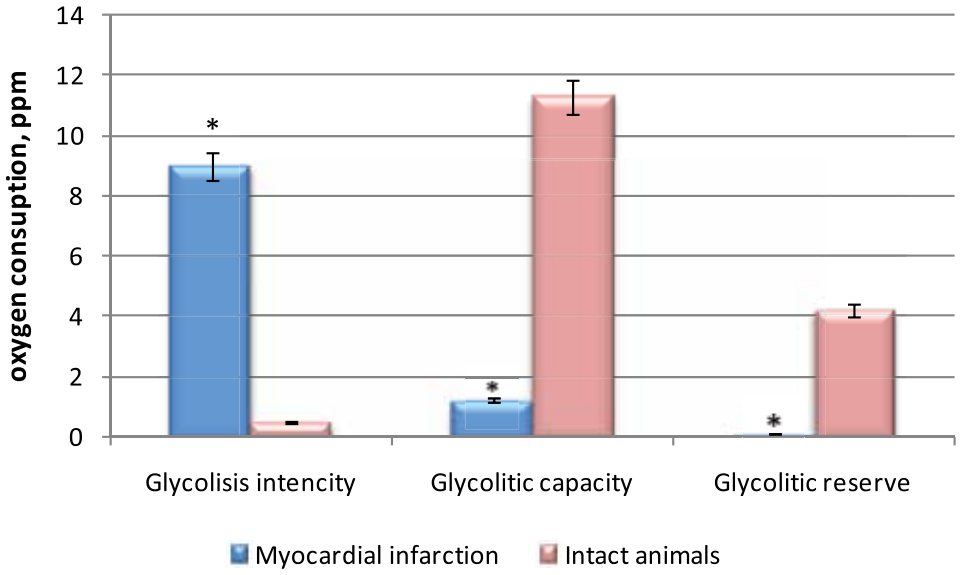

Figure 5. Assessment of changes in the glycolysis process in myocardial infarction conditions

*Note: * – statistically significant relative to the group of intact animals (Newman- Keuls test, $p < 0.05$)*

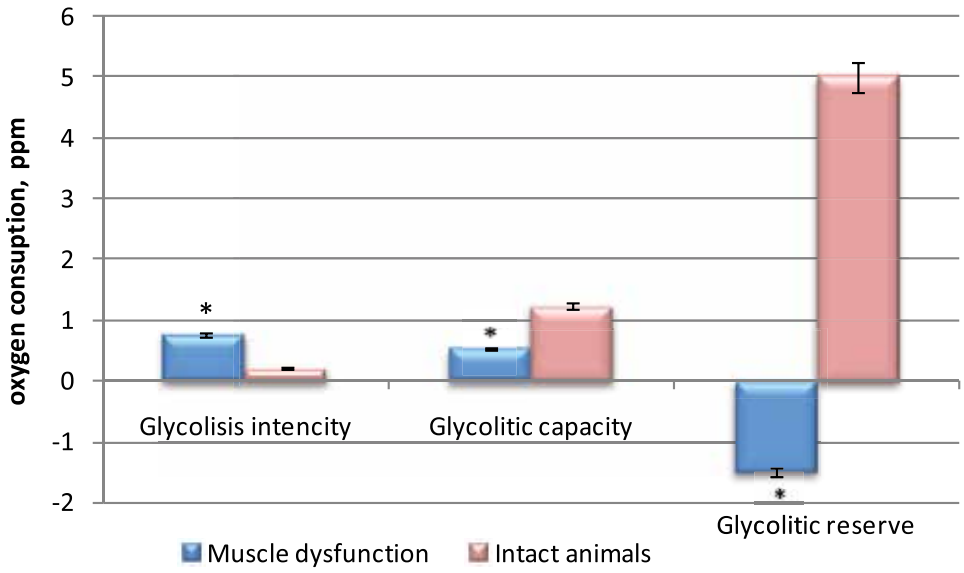

Figure 6. Assessment of changes in the glycolysis process in muscle dysfunction conditions

*Note: * – statistically significant relative to the group of intact animals (Newman- Keuls test, $p < 0.05$)*

ОРИГИНАЛЬНАЯ СТАТЬЯ
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In rats, against the background of muscle dysfunction (Fig. 6), in comparison with intact animals, an increase in glycolysis intensity was observed, as well as a decrease in glycolytic capacity by 3.55 times (p <0.05) and by 2.35 times (p <0.05) , while the value of the glycolytic reserve took a negative value.

Evaluating the change in the activity of the mitochondrial respiratory chain complexes, it was found out that in rats under conditions of cerebral ischemia (Fig. 7) a decrease in the activity of mitochondrial complexes I, II, IV and V was observed in comparison with the intact group of rats by 4.8 (p <0.05 a) times; by 4.6 times (p <0.05); by 13.4 times (p <0.05) and by 9.33 times (p <0.05, respectively. Against the background of experimentally modeled TBI (Fig. 7), in animals relative to the intact group of rats, a decrease in the activity of complex I by 2.17 times (p <0.05), complex II – by 4.8 times (p <0.05), complex IV – by 11.1 times (p <0.05) and complex V – 8.1 by times (p <0.05) was observed.

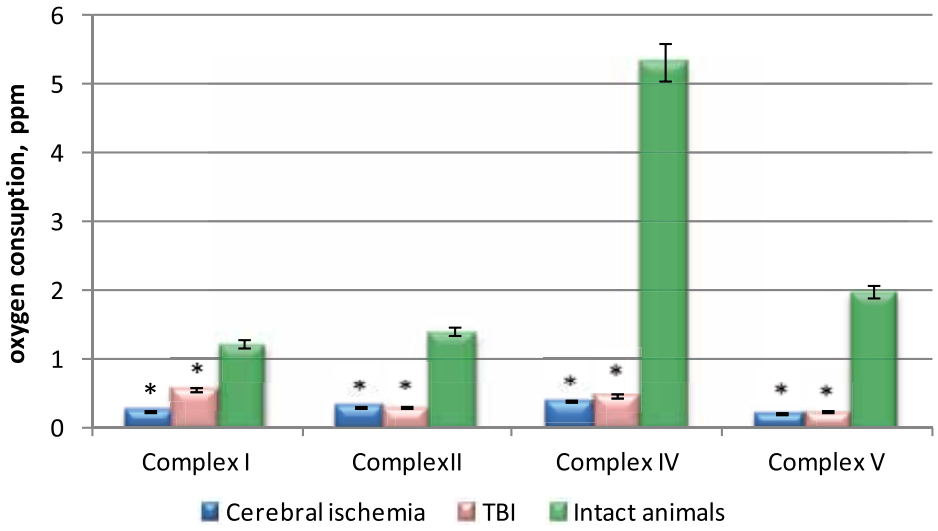

Figure 7. Evaluation of changes in the activity of the mitochondrial respiratory chain complexes under conditions of experimental cerebral ischemia and traumatic brain injury

*Note: * – statistically significant relative to the group of intact animals (Newman- Keuls test, p <0.05)*

Under conditions of myocardial infarction (Fig. 8), the animals showed a decrease in the activity of mitochondrial complexes I, II, IV and V in comparison with intact animals by 3.3 times (p <0.05); by 3.4 times (p <0.05); by 11.1 times (p <0.05) and by 7.5 times (p <0.05), respectively.

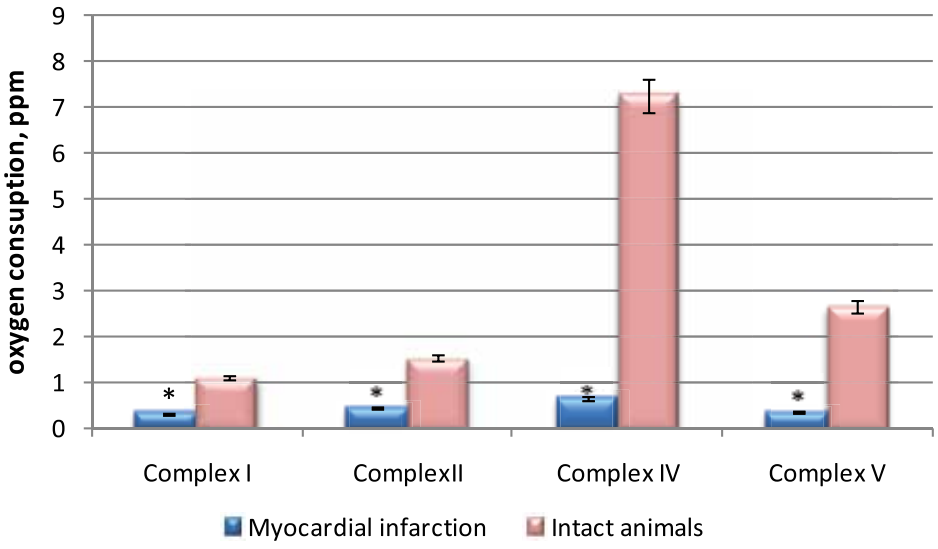

Figure 8. Evaluation of changes in the activity of the mitochondrial respiratory chain complexes under conditions of experimental myocardial infarction

*Note: * – statistically significant relative to the group of intact animals (Newman- Keuls test, p <0.05)*

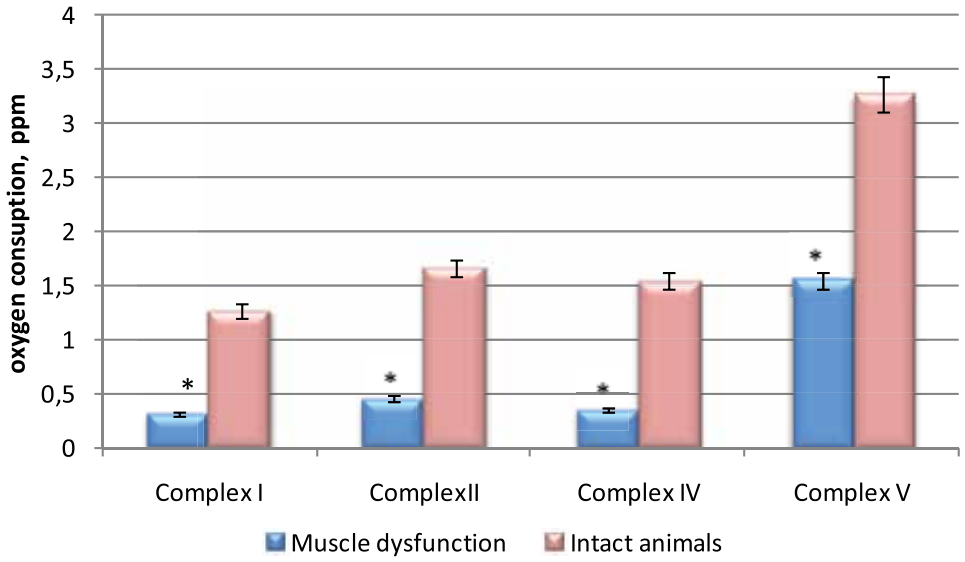

Figure 9. Evaluation of changes in the activity of the mitochondrial respiratory chain complexes under conditions of experimental muscle dysfunction

*Note: * – statistically significant relative to the group of intact animals (Newman- Keuls test, p <0.05)*

In animals with muscle dysfunction (Fig. 9), the activity of the respiratory complexes I, II, IV and V was 4 times lower in comparison with the intact rats (p <0.05); 3.6 times (p <0.05); 4.3 times (p <0.05) and 2.1 times (p <0.05), respectively.

Assessing the change in the concentration of enzyme complexes characterizing mitochondrial function (Table 1), it was found out that NOX4 activity increases in groups of animals with model pathologies: cerebral ischemia, TBI, myocardial infarction and muscle dysfunction compared to the group of the intact rats by 15.8 times (p <0.05); by 10.2 times (p <0.05); by 9.2 times (p <0.05) and by 6.1 times (p <0.05), respectively. In animals with experimentally reproduced cerebral ischemia, a decrease in CoX and mATP activity was also observed relative to the group of the intact rats by 2.9 times (p <0.05) and by 3.4 times (p <0.05), respectively.

Table 1. Change in the concentration of mitochondrial function markers under conditions of various pathologies (ELISA study)

Group	NOX4, ng/ml	CoX, ng/ml	mATP, ng/ml	ATP ng/ml
Intact animals (Brain)	1.2±0.014	46.97±0.695	98.62±2.631	1172.34±10.291
TBI	12.23±0.237*	26.4±0.896*	36.3±1.917*	453.1±8.614*
Cerebral ischemia	18.1±0.331*	16.35±0.417*	29.1±1.118*	364.61±7.924*
Intact animals (Myocardium)	1,6±0.028	43.94±0.792	101.2±2.939	1233.1±9.144
Myocardial infarction	14.75±0.542*	28.6±0.991*	43.2±1.249*	662.4±5.271*
Intact animals (Muscle tissue)	2.65±0.634	48.91±0.541	109.24±1.712	1536.2±8.176
Muscle dysfunction	16.2±0.524±0.743*	27.5±0.335*	18.6±2.364*	379.65±6.928*

*Note: * – statistically significant relative to the group of intact animals (Newman-Keuls test, p <0.05)*

At the same time, in animals with TBI, the content of Cox and mATP, in comparison with intact rats decreased by 1.8 times (p <0.05) and 2.7 times (p <0.05), , respectively. Under the conditions of myocardial infarction (Table 1), the rats showed a decrease in CoX and mATP activity relative to the intact group of animals by 1.5 times (p <0.05) and by 2.3 times (p <0.05), respectively. Besides, against the background of experimental

ОРИГИНАЛЬНАЯ СТАТЬЯ
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muscle dysfunction (Table 1), the content of these enzymes also decreased (compared to the intact group of rats: CoX – by 1.8 times ($p < 0.05$); mATP – by 5.9 times ($p < 0,05$)). It is quite important that the observed negative changes in mitochondrial function under conditions of cerebral ischemia, TBI, myocardial infarction and muscle dysfunction were accompanied by a decrease in ATP concentration relative to intact rats by 3.2 times ($p < 0.05$); by 2.6 times ($p < 0.05$); by 1.8 times ($p < 0.05$) and by 4 times ($p < 0.05$), respectively.

DISCUSSION

Currently, it has been established that a significant number of pathologies are associated with the development of mitochondrial dysfunction [18]. Mitochondrial dysfunction is an integral part of the etiopathogeneses of various diseases, however, mitochondrial dysfunction plays the most important role in the development and progression of pathologies of the brain, heart and skeletal muscles – most energy-intensive organs, functioning of which requires a constant sum of macroergs [19–21]. The present study focused on the evaluationt of mitochondrial respiration function under conditions of ischemic genesis pathologies, in which there is a significant energy deficit that directly characterizes the activity of mitochondria – focal ischemia, brain injury, myocardial infarction and muscle dysfunction [22]. The study has shown that under conditions of model pathologies, there is a significant deterioration in the ATP-synthetic ability of mitochondria, which reflects a decrease in the maximum level of respiration, respiratory capacity and ATP-generating ability of mitochondria in comparison with intact animals [23]. At the same time, it is important that the decrease in the ATP-synthesizing function of mitochondria was accompanied by the intensification of glycolysis processes which was not compensated, and had a maximum permissible nature. It can be judged by a significant decrease in glycolytic capacity, glycolytic reserve and ATP concentration in the animals with model pathologies relative to the intact rats [24]. In addition, dysfunction of mitochondrial complexes I, II, IV and V was observed in animals against the background of the pathological processes of the brain, myocardium and muscles, which, ultimately, had a negative effect on the process of electron transfer in the mitochondrial respiratory chain [25]. NOX4 indicates a significant decrease in the electron transport potential of complexes I and II, with an increasing prooxidant potential of the cell [26]. It is known that when it is impossible to directly transport oxygen in the mitochondrial respiratory chain, the oxidizer is metabolized in an alternative way with activation of NADPH oxidase and in particular NOX4, resulting in a significant increase in the intracellular concentration of the superoxide radical that triggers oxidative stress [27]. Subsequently, the termination of electron transfer in complexes IV and V (confirmed by a decrease in CoX and mATP activity) hinders the conversion of ADP to ATP, and as a result, the total pool of high-energy compounds decreases, requiring an increase in glycolysis processes, which has been also established by this study and is consistent with the literature data [28].

CONCLUSION

Based on the data obtained, a significant deterioration of the mitochondrial respirometric function under conditions of ischemic brain, myocardial and skeletal musculature, accompanied by dissociation of electron transfer in the mitochondrial respiratory chain (dysfunction of complexes I, II, IV and V), decrease in ATP-synthesizing ability of mitochondria and the reinforcement of the glycolysis processes of a limiting nature can be supposed. In this case, probably, the correction of the mitochondrial respiratory function may be a new strategy for the treatment of ischemic conditions, which allows the targeted therapeutic effect to level the energy deficit and the mechanisms of cellular damage associated with it under ischemia.

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ОРИГИНАЛЬНАЯ СТАТЬЯ
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Conflict of interest

The authors declare no conflict of interest.

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