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# METABOLIC EFFECTS OF LONG-TERM EXPOSURE TO WAVE-LIKE OXYGEN FASTING OF MODERATE SEVERITY

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**Abstract.** ***Relevance.*** A variety of oxygen-dependent pathological conditions include intermittent, undulating episodes of hypoxia, alternating with a person's stay in normoxia. An example of such conditions is sleep apnea. The features of metabolism in such conditions have not been practically studied, which determines the relevance of the study. ***Purpose of the study:*** to reveal the features of metabolism in laboratory animals subjected to chronic undulating oxygen starvation in order to improve the diagnostic criteria for the consequences of intermittent hypoxia. ***Materials and methods.*** Long-term undulating normobaric hypoxia was created in a BIO-NOVA-2004 membrane hypoxicator (Moscow), adapted to work with rodents. The following operating mode of the hypoxicator was used — an air gas mixture with an oxygen content of 14%, the duration of a single hypoxic cycle is 60 minutes, the interval between cycles is 30 minutes, the number of cycles per day is 6 (the total period of moderate hypoxia is 6 hours per day), the duration of daily hypoxic exposure is 24 weeks. Laboratory animals (female mice of the C57BL/6J line) were obtained from the nursery of laboratory animals "Rappolovo" (Leningrad region). The animals were kept in a certified vivarium in accordance with the requirements of GOST 33044-2014 of August 1, 2015 "Principles of Good Laboratory Practice" and Order of the Ministry of Health of the Russian Federation of April 1, 2016 No. 267 "On Approval of the Rules of Good Laboratory Practice". Biological material for research (blood, tissues) was taken from animals on the next day after the cessation of hypoxic exposure. In the blood serum, the activity of the liver enzymes AlAT, AST, GGTP, the levels of total cholesterol, low-density lipoproteins and triglycerides, and the concentration of glucose were determined. In addition, the content of neutral and basic carbonyl groups of proteins was determined in blood serum, and the activity of SOD and catalase (CAT) in erythrocytes was determined. In the liver tissue, the carbonyl groups of proteins, the content of total lipids and glycogen were determined; in skeletal muscles — glycogen. Statistical processing of the obtained data was carried out using the application package for data analysis (MS Windows 10) using the methods of correlation and dispersion analysis. Differences were considered significant at $p < 0.05$. ***Results.*** The most pronounced changes in biochemical parameters after prolonged exposure to wave-like moderate oxygen starvation are observed in cellular structures (liver, skeletal muscles, erythrocytes), while the parameters recorded in the blood plasma of animals were resistant to intermittent hypoxic exposure. ***Conclusion.*** The energy deficiency that occurs during chronic wave-like oxygen deficiency manifests itself in the mobilization of carbohydrate reserves of the body, which was accompanied by a 4–5-fold decrease in glycogen in the liver and skeletal muscles and the involvement of lipids as energy production substrates (a decrease in lipids in the liver by 27%), switching the flow of amino acids to other types of exchange (decrease in GGTP activity by 14%). The resulting oxygen deficiency

was naturally accompanied by a decrease in the activity of SOD by almost 1000 times and catalase by 4 times, the accumulation of underoxidized products (an increase in the content of basic carbonyl groups in blood proteins by 41%).

**Key words:** metabolism: hypoxia: liver lipids: glycogen: laboratory animals; obstructive sleep apnea.

# МЕТАБОЛИЧЕСКИЕ ЭФФЕКТЫ ДЛИТЕЛЬНОГО ВОЗДЕЙСТВИЯ ВОЛНООБРАЗНОГО КИСЛОРОДНОГО ГОЛОДАНИЯ УМЕРЕННОЙ СТЕПЕНИ ТЯЖЕСТИ

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**Резюме.** ***Актуальность.*** К числу разнообразных кислородзависимых патологических состояний относят, в том числе, интермиттирующие, волнообразно протекающие эпизоды гипоксии, чередующиеся с пребыванием человека в условиях нормоксии. Примером подобных состояний является сонное апноэ. Особенности метаболизма при таких состояниях практически не изучались, что и определяет актуальность исследования. ***Цель исследования:*** выявить особенности метаболизма у лабораторных животных, подвергающихся хроническому волнообразному кислородному голоданию, для совершенствования диагностических критериев последствий интермиттирующей гипоксии. ***Материалы и методы.*** Длительная волнообразная нормобарическая гипоксия создавалась в мембранном гипоксикаторе БИО-НОВА-2004 (Москва), адаптированном для работы с грызунами. Использовался следующий режим работы гипоксикатора: воздушная газовая смесь с содержанием кислорода 14%, продолжительность единичного гипоксического цикла — 60 минут, интервал между циклами — 30 минут, число циклов в сутки — 6 (суммарный период умеренной гипоксии — 6 часов в сутки), длительность ежедневного гипоксического воздействия — 24 недели. Лабораторные животные (мыши-самцы линии C57BL/6J) были получены из питомника лабораторных животных «Рапполово» (Ленинградская обл.). Содержание животных осуществлялось в условиях сертифицированного вивария в соответствии с требованиями ГОСТ 33044-2014 от 01.08.2015 г. «Принципы надлежащей лабораторной практики» и приказа МЗ РФ от 01.04.2016 г. № 267 «Об утверждении Правил надлежащей лабораторной практики». Биологический материал для исследования (кровь, ткани) у животных забирали на следующие сутки после прекращения гипоксического воздействия. В сыворотке крови определяли активность печеночных ферментов аланинаминотрансфераза (АЛТ), аспартатаминотрансфераза (АСТ), гамма-глутамилтранспептидаза (ГГТП), уровни общего холестерина, липопротеидов низкой плотности и триглицеридов, концентрацию глюкозы. Кроме того, в сыворотке крови определяли содержание нейтральных и основных карбонильных групп белков, а в эритроцитах — активность супероксиддисмутазы (СОД) и каталазы (КАТ). В ткани печени определяли карбонильные группировки белков, содержание суммарных липидов и гликогена; в скелетных мышцах — гликогена. Статистическая обработка полученных данных осуществлялась с помощью прикладного пакета программ для анализа данных (MS Windows 10) с применением методов корреляционного и дисперсионного анализа. Различия считались достоверными при $p < 0,05$. ***Результаты.*** Наиболее выраженные изменения в биохимических показателях после длительного воздействия волнообразного умеренного кислородного голодания отмечаются в клеточных структурах (печень, скелетные мышцы, эритроциты), в то время как показатели, регистрируемые в плазме крови животных, были устойчивы к прерывистому гипоксическому воздействию. ***Заключение.*** Возникающий при хронической волнообразной

кислородной недостаточности энергодефицит проявлялся в мобилизации углеводных резервов организма, что сопровождалось снижением гликогена в печени и скелетных мышцах в 4–5 раз и вовлечением липидов в качестве субстратов энергопродукции (снижение липидов в печени на 27%), переключением потока аминокислот на другие виды обмена (снижение активности ГГТП на 14%). Возникающий дефицит кислорода закономерно сопровождался снижением активности СОД практически в 1000 раз и каталазы в 4 раза, накоплением недоокисленных продуктов (повышение содержания основных карбонильных группировок в белках крови на 41%).

***Ключевые слова:*** метаболизм; гипоксия; липиды печени; гликоген; лабораторные животные; обструктивное апноэ сна.

## INTRODUCTION

In clinical practise, there is a lot of situations, when a person is in hypoxia for a long time. Such cases are, firstly, obstructive sleep apnoea, hypoxia in chronic obstructive pulmonary disease, chronic heart failure, respiratory failure after chest surgery, chronic discirculatory cerebrovascular disorders. Specific features of chronic intermittent hypoxia are protracted course, alternation of hypoxic and normoxic conditions, moderate hypoxia, undulating changes in the severity of the condition.

It should be noted, that main literature sources on intermittent hypoxia are about obstructive sleep apnoea and its role in the risks of development of cardiovascular [1–3], endocrinological disorders and metabolic syndrome [4]. Systemic issues of the impact of intermittent hypoxia on the body are shown in number of reviews [5–7].

The development of modern approaches to the treatment of complications and remote consequences of intermittent therapy requires a large volume of biomedical research. In the practice of preclinical studies, private methods of modelling clinically significant pathological processes are widely used. At the same time, they are not optimal in terms of assessing the significance of the hypoxic component of pathogenesis. In this regard, an experimental model of chronic intermittent hypoxia [8] was used, created by the method of chronic intermittent normobaric hypoxic exposure.

Long-term intermittent hypoxic impact may be used to assess the consequences, including behavioural, metabolic, immune, and other, associated with long-term undulating impact of moderate hypoxia on animals. So, the aim of the study is to identify features of metabolic reactions in laboratory animals exposed in chronic undulating hypoxia, and to improve diagnostic criteria for intermittent hypoxia and its consequences.

## MATERIALS AND METHODS

Normobaric hypoxia was created using a BIO-NOVA-2004 membrane hypoxicator (Moscow), adapted for work with rodents. The following intermittent hypoxia regime was established: oxygen content in the hypoxic gas chamber was 14 %, duration of a single hypoxic cycle was 60 minutes, an interval between cycles was 30 minutes, the number of cycles per day was 6 (total period of moderate hypoxia was 6 hours per day), duration of daily hypoxic exposure was 24 weeks.

Laboratory animals (male mice of the C57BL/6J line) were obtained from the Federal State Unitary Enterprise LAN Rappolovo (Leningrad Region). The animals were kept in a certified vivarium in accordance with the requirements of GOST 33044-2014 dated 01.08.2015 “Principles of Good Laboratory Practice” and the order of the Ministry of Health of the Russian Federation dated 01.04.2016 N 267 “On approval of the Rules of Good Laboratory Practice”.

The laboratory animals were randomised into two groups after 14-days of quarantine: controls and a group affected by hypoxia. A biological material for the research (blood, tissues) was collected the next day after the end of hypoxic exposure. At the end of the experiment, blood was collected from animals anesthetised with chloral hydrate using cardiac puncture into test tubes with a blood coagulation activator. After 30 minutes of settling, the blood was centrifuged for 10 minutes at 1000 rpm, the resulting serum was separated, and then centrifuged second time at 4000 rpm for 15 minutes. Then, the serum was transferred into secondary test tubes and located into analyser. Using standard methods of the biochemical analysers Stat Fax 1904 + (USA) and Erba Lachema (Czech Republic), ALT, AST, GGT, levels of cholesterol, low-density lipoproteins (LDL), triglycerides, glucose concentration were determined. Moreover, the content of neutral and basic carbonyl groups of proteins in blood serum, and activity of SOD and catalase in erythrocytes was determined. Carbonyl groups of liver proteins were determined by the reaction of oxidised amino acid residues of proteins with 2,4-dinitrophenylhydrazine (DNPH) with the formation of coloured hydrazones [9–11]. The content of total lipids and glycogen was determined in liver tissue. Also, glycogen was determined in skeletal muscles. Glycogen in liver and muscles was determined using the method [12]. Quantitative determination of total lipids in liver was performed using the Folch method [13].

## RESULTS

In control animals, the studied metabolic indices formed several groups of correlating indices (Fig. 1, 2). The first group may

be conventionally designated as a lipid factor (Fig. 1), including such indices as liver lipids, cholesterol, triglycerides, ALT, AST, GGT and liver glycogen. The second group of indices consists of blood glucose, muscle glycogen and LDL. Such factor may be interpreted as carbohydrate one. The third group consists of indicators of the content of carbonyl groups (neutral and base) in blood proteins. They closely correlate with each other (r = + 0.96). An independent index, not associated with other studied metabolic indices, is SOD activity.

Table 1 demonstrates the results of the study of the metabolic consequences of prolonged exposure to moderate intermittent hypoxia.

The analysed parameters are heterogeneous in terms of sensitivity to long-term intermittent moderate hypoxia. A number of metabolic parameters obtained from blood serum are practically insensitive to this effect (ALT, cholesterol, LDL, triglycerides, neutral carboxyl groups of blood proteins). A moderate but statistically insignificant increase was noted for AST and the basic carboxyl groups of blood proteins. The content of glucose and GGTP in serum significantly decreased.

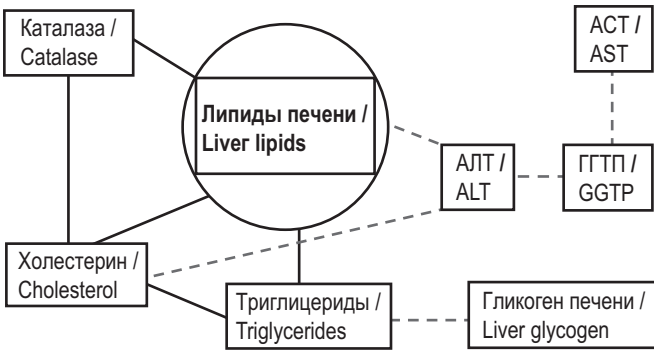


**Fig. 1. A graph of correlation links of lipid factor in intact animals. Designations: continuous line — moderate positive correlations, dotted line — moderate negative correlations. ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGTP — gamma-glutamyl transpeptidase**

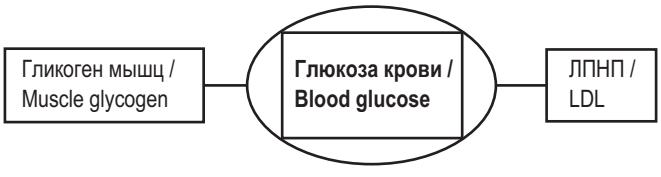


**Fig. 2. A graph of correlation links of carbohydrate factor in intact animals. Designations: continuous line — moderate positive correlations. LDL — low-density lipoproteins**

*Table 1*

**Changes in the metabolic parameters of laboratory animals under the influence of prolonged undulating (intermittent) moderate hypoxia**

*Таблица 1*

**Изменения метаболических показателей лабораторных животных под влиянием длительной волнообразной (прерывистой) умеренной гипоксии**

| Parameter | Unit of measurement | Values in groups (M ± m) | | Influence of hypoxia, % | Reliability of differences, p |
|---|---|---|---|---|---|
| | | intact | hypoxia | | |
| In blood plasma | | | | | |
| Glucose | mmol/l | 8,3 ± 0,8 | 5,2 ± 0,8 | **–37** | **0,03** |
| ALT | IU/ml | 22,9 ± 2,6 | 25,0 ± 2,6 | + 9 | 0,60 |
| AST | IU/ml | 65,7 ± 7,3 | 78,8 ± 9,4 | + 20 | 0,29 |
| GGTP | IU/ml | 0,36 ± 0,09 | 0,05 ± 0,03 | **–86** | **0,02** |
| Cholesterol | mmol/l | 1,24 ± 0,09 | 1,23 ± 0,12 | –1 | 0,95 |
| LDL | mmol/l | 0,23 ± 0,03 | 0,22 ± 0,04 | –4 | 0,84 |
| Triglycerides | mmol/l | 0,39 ± 0,05 | 0,40 ± 0,03 | + 2 | 0,92 |
| Neutral carbonyl groups | D370/mg of protein | 2,18 ± 0,17 | 2,26 ± 0,28 | + 4 | 0,80 |
| Basic carbonyl groups | D430/mg of protein | 0,62 ± 0,06 | 0,88 ± 0,15 | **+ 41** | **0,08** |
| In erythrocytes | | | | | |
| SOD | su/ml blood | 34,2 ± 1,7 | 0,05 ± 0,01 | **–99,8** | **$3 \times 10^{-10}$** |
| Catalase | Mmol $H_2O_2 \times 10^3$/ min × ml of blood | 22,5 ± 0,5 | 5,7 ± 0,3 | **–75** | **$2 \times 10^{-13}$** |
| In tissues | | | | | |
| Liver lipids | mg/g of tissue | 0,06 ± 0,01 | 0,05 ± 0,01 | **–27** | **0,0001** |
| Liver glycogen | mg/g of tissue | 0,90 ± 0,06 | 0,19 ± 0,02 | **–80** | **$8 \times 10^{-7}$** |
| Muscle glycogen | mg/g of tissue | 0,40 ± 0,02 | 0,09 ± 0,01 | **–76** | **$2 \times 10^{-8}$** |

**Note:** Significant effects associated with hypoxic exposure are highlighted in bold.

The most pronounced metabolic response was typical for indices of erythrocytes (a sharp decrease in SOD, catalase) and tissues (a sharp decrease in liver lipase, and glycogen both in liver and muscles).

A restructuring of the correlation links occurs under the conditions of hypoxia. The links are combined into one factor with a significant increase in the links density (Fig. 3). Such phenomenon allows to interpret these indices taken together as a factor of metabolic stress. The restructuring of the main correlation links of the studied metabolic parameters under the influence of long-term intermittent exposure to hypoxia is shown in Table 2.

Specific effects of metabolic consequences of long-term intermitted hypoxic exposure are manifested both by the destruction of old and emergence of new correlation links. Destruction of correlation links typical for the control animals is noted for liver lipids (with catalase, cholesterol and triglycerides), glucose (with muscle glycogen and LDL), cholesterol, and ALT levels. It reflects the impossibility of the previous course of typical reactions of carbohydrate and lipid synthesis, most likely due to chronic energy deficiency. The most interesting is the destruction of the link between the blood glucose level and muscle glycogen level. This indicates a radical restructuring of muscle energy metabolism. The main source of energy for this becomes the utilisation of amino acids, and the source of glucose for maintaining the glycogen level is the gluconeogenesis reaction, but not the capture of glucose from blood due to chronic glucose deficiency.

Under the influence of long-term intermittent hypoxic exposure, new correlations begin to appear in laboratory animals, indicating the formation of new metabolic "templates" of the body associated with the parameters of lipid metabolism. A new correlation between the levels of liver lipids and blood glucose, cholesterol and muscle glycogen is noteworthy. Such correlations may indicate more intensive involvement of lipids in metabolic processes compared to normoxic conditions. Of particular interest is also the emerging negative correlation between the activity of indicators of antioxidant defense enzymes (SOD, catalase). It reflects the inhibition of its activity during the accumulation of lipid peroxidation products (LPO), although under normal conditions these enzymes are largely substrate-activated and do not affect each other's activity.

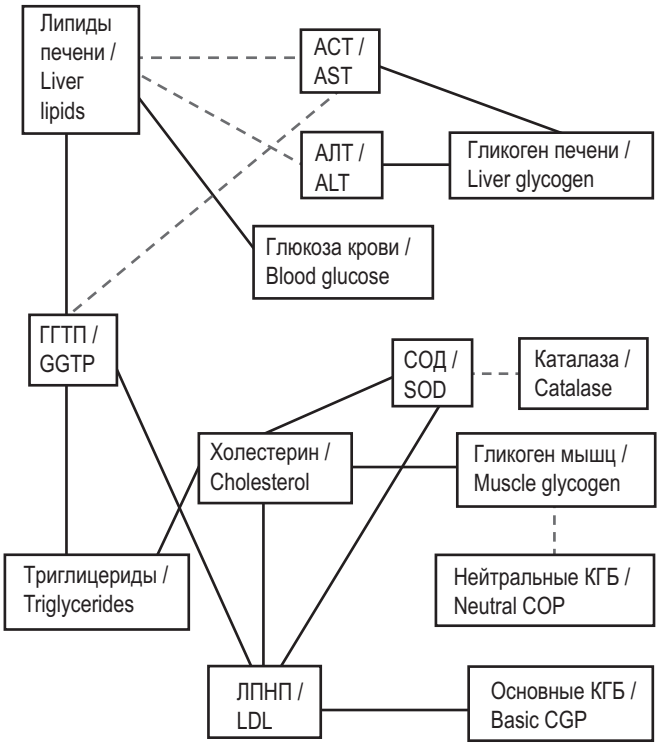


**Fig. 3. A graph of correlations of metabolic parameters after long-term exposure to intermittent moderate hypoxia. Designations: continuous line — moderate positive correlations, dotted line — moderate negative correlations. ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGTP — gamma-glutamyl transpeptidase; CGRP — protein carbonyl groups; LDL — low-density lipoproteins; SOD — superoxide dismutase.**

## DISCUSSION

We have not found any similar studies on the issue of changes in metabolism under the conditions of long-term intermittent hypoxia in laboratory animals. Probably, this is due to the difficulties in correct modelling of such condition, the lack of validated and standardised methods for its modelling, variability in the duration of hypoxic exposure and its severity. Nevertheless, the number of studies should be noted, that allows to compare our results with data of other authors. So, in one study [14], an ability of a 10-day cycle of interval hypoxic training to normalise LPO processes and increase the activity of suppressed antioxidant enzymes has been demonstrated. At the same time, in our study, which was much longer, the deficiency of oxygen appeared under the conditions of chronic hypoxia was leaded by suppression of antioxidant system (a decrease in SOD activity by almost 1000 times and catalase by 4 times). Also, there was an accumulation of under-oxidised products (an increase in the content of basic carbonyl groups in blood proteins by 41 %). This discrepancy in the dynamics of LPO and antioxidant system (AOS) indicators shows that the mechanisms underlying the short-term rehabilitation effect on the human body during interval training are fundamentally different from the pathogenetic mechanisms of long-term (28 weeks) exposure to intermittent hypoxia.

*Table 2*

**Restructuring of correlations of metabolic parameters under the influence of long-term intermittent exposure to hypoxia**

*Таблица 2*

**Перестройка корреляционных связей метаболических показателей под влиянием длительного прерывистого воздействия гипоксии**

| Parameter A | Parameter B | Correlation coefficients | | Effect of hypoxia |
|---|---|---|---|---|
| | | normal oxygen content | hypoxia | |
| Liver lipids | Catalase | + 0,58 | + 0,24 | Destruction |
| Liver lipids | Cholesterol | + 0,68 | + 0,22 | Destruction |
| Liver lipids | Triglycerides | + 0,50 | + 0,27 | Destruction |
| Liver lipids | ALT | -0,52 | –0,76 | Gain |
| Liver lipids | Glucose | + 0,02 | + 0,83 | Appearance |
| Liver lipids | GGTP | + 0,23 | + 0,84 | Appearance |
| Liver lipids | AST | + 0,36 | –0,73 | Appearance |
| Liver lipids | Neutral carbonyl groups | + 0,01 | –0,54 | Appearance |
| Cholesterol | Triglycerides | + 0,88 | + 0,70 | Maintaining |
| Cholesterol | Muscle glycogen | + 0,03 | + 0,66 | Appearance |
| Cholesterol | LDL | –0,05 | + 0,95 | Appearance |
| Cholesterol | SOD | –0,09 | + 0,67 | Appearance |
| Cholesterol | ALT | –0,66 | 0,01 | Destruction |
| ALT | GGTP | –0,57 | –0,80 | Gain |
| ALT | AST | + 0,20 | –0,80 | Appearance |
| ALT | liver glycogen | + 0,38 | + 0,54 | Gain |
| AST | GGTP | –0,64 | –0,49 | Weakening |
| AST | liver glycogen | 0,06 | + 0,64 | Appearance |
| ACT/ AST | Neutral carbonyl groups | –0,23 | + 0,69 | Appearance |
| GGTP | Triglycerides | + 0,37 | + 0,61 | Gain |
| GGTP | LDL | + 0,16 | + 0,61 | Appearance |
| LDL | Muscle glycogen | –0,38 | + 0,68 | Inversion |
| LDL | Basic carbonyl groups | –0,31 | + 0,58 | Inversion |
| LDL | SOD | –0,39 | + 0,55 | Inversion |
| LDL | Glucose | + 0,66 | –0,19 | Destruction |
| Muscle glycogen | Glucose | + 0,58 | –0,10 | Destruction |
| Muscle glycogen | Neutral carbonyl groups | + 0,49 | –0,68 | Inversion |
| Muscle glycogen | Triglycerides | –0,58 | + 0,72 | Inversion |
| SOD | Catalase | + 0,25 | –0,84 | Appearance |
| Neutral carbonyl groups | Basic carbonyl groups | + 0,96 | + 0,45 | Weakening |

The study [15] provides data on the interaction between different regulatory systems of the brain in obstructive sleep apnoea, aimed at the discordance of vegetative and endocrine regulation of basal metabolism, eating behaviour, regulation of heart and blood vessels, restructuring of carbohydrate and lipid metabolism in muscles, liver and adipocytes, including those mediated by pro-inflammatory cytokines. In principle, our data do not contradict the cited works.

## CONCLUSION

The most pronounced changes in biochemical indices after prolonged exposure to intermittent moderate hypoxia are observed in cellular structures (liver cells, skeletal muscles, erythrocytes). At the same time, the indices recorded in blood serum of animals, probably due to homeostatic mechanisms, are much more resistant to intermittent hypoxic effects. This

is natural, since it is the energy processes occurring in cells that are the object of hypoxia, and the consequences of chronic undulation (intermittent) hypoxic effects should also have predominantly intracellular localisation. Thus, energy deficiency that occurs with chronic hypoxia is primarily manifested in the mobilisation of carbohydrate reserves of the body. This is manifested by a decrease in glycogen in cells of liver and skeletal muscles by 4–5 times. However, even such powerful activation of glycolytic reactions in tissues is insufficient to compensate for energy deficiency. This causes additional utilisation of blood glucose (a decrease of 37 %) and the involvement of lipids as substrates for energy production (a decrease in the lipid content in the liver by 27 %), switching the flow of amino acids from non-phosphorylating detoxification processes to other types of metabolism (a decrease in the activity of substrate-dependent enzyme of GGT detoxification by 14 %).

Thus, the shifts reflect fairly profound changes in the functioning of energy-providing mechanisms of cells in response to long-term intermittent hypoxic exposure.

## ADDITIONAL INFORMATION

**Author contribution.** Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

**Competing interests.** The authors declare that they have no competing interests.

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**Experiments with animals** were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

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