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# FATTY ACIDS COMPOSITION OF INNER MITOCHONDRIAL MEMBRANE OF RAT CARDIOMYOCYTES AND HEPATOCYTES DURING HYPOXIA-HYPERCAPNIA

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*We studied the influence of hypoxic-hypercapnic environment under the effect of hypothermia (artificial hibernation) on fatty acids spectrum of inner mitochondrial membrane (IMM) lipids of rat cardiomyocytes and hepatocytes. Specific for cellular organelles redistribution of IMM fatty acids was determined. It led to the reduction of total amount of saturated fatty acids (SFAs) and increase of unsaturated fatty acids (UFAs) in cardiomyocytes and to the increase of SFAs and decrease of UFAs in hepatocytes. The decrease in the content of oleic acid and increased content of arachidonic and docosahexaenoic acids in IMM were shown. This may be due to their role in the regulatory systems during hibernation, as well as following exit therefrom. It is assumed that artificial hibernation state is characterized by the stress reaction leading to optimal readjustment of fatty acids composition of membrane lipids, which supports functional activity of mitochondria in hepatocytes and cardiomyocytes.*

*K e y w o r d s: saturated and unsaturated fatty acids, inner mitochondrial membrane, hepatocytes, cardiomyocytes, hypoxia, hypercapnia, hypothermia.*

Chemical composition of phospholipids that are structural components of cell membranes plays an important role in their functioning and various processes in cells. In particular, saturated fatty acids (SFAs) are the main energy substrate for cardiomyocytes. Unsaturated fatty acids (UFAs), due to their ability to increase the degree of unsaturation in phospholipid acyl chains and reduce microviscosity of cellular membranes, are very important in the regulation of membrane permeability and functioning of membrane-bound proteins. In addition, certain UFAs are precursors of physiologically active substances, such as eicosanoids [1].

Modification of lipid composition, affecting the intensity of metabolism, acts as a compensatory mechanism that provides functionality of membrane under various conditions. Particularly, changes in ambient temperature, hypoxia, etc. lead to certain shifts in the composition of eukaryotic membrane lipids [2, 3]. The study of animal adaptations to different environmental conditions remains current issue of theoretical and practical biology.

Non-hibernating mammals influenced by hypothermia in hypoxic-hypercapnic gaseous medium fall into so-called cold narcosis or artificial hibernation state. This results in reduction of metabolic rate along with changes in bioenergetic processes in tissues and mitochondria [4, 5].

The main suppliers of energy stored in the form of ATP in eukaryotic cells are mitochondria. Their functional activity is provided by the inner membrane which contains components of the electron transport chain and ATP synthase that are needed to transform the energy of electrons transfer for ATP synthesis. This energy is crucial for specific cellular functions, including response formation to external stimuli [6]. The matter of particular interest is the study of the role of lipids in mitochondrial membranes adaptation to extreme conditions. Due to the changes in concentration and ratio of fatty acids, lipid composition of membranes undergoes reorganization, creating optimal conditions for preserving functional activity of intracellular organelles in particular and cells in general [7].

The studies of temperature adaptation of homeotherms indicate the regulatory role of lipids in hibernation. However, natural and artificial hibernation affect the lipid composition of cell membranes of mammals in different ways [8]. In addition, existing data on the effects of low temperatures or artificial hibernation on the chemical composition of lipids in mammals tissues are uncertain.

The goal of the research was estimation of fatty acids composition in inner mitochondrial membrane (IMM) lipids of cardiomyocytes and hepatocytes of rats during artificial hibernation (the effect of hypothermia, hypercapnia and hypoxia) and after exit from the hibernation.

## Materials and Methods

42 white male outbred rats weighing 180-200 g were used in the experiments. Experiments were performed according to the requirements of European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986).

The animals were grouped as follows: 1st - control group (intact animals), 2nd - rats under artificial hibernation, 3rd - animals 24 h after exit from artificial hibernation. This condition was created according to Bakhmetiev-Dzay-Anzhus, combining hypoxic-hypercapnic influence with external cooling as described in detail [9].

The animals were placed into a hermetically closed chamber with the volume of 3 L at 3-4 °C. The animals developed hypobiotic state during 3-3.5 h of stay in the chamber; their body temperature lowered to 16 °C. The animals were decapitated in three different conditions: in state of normothemia (body temperature 37 °C), during artificial hibernation (body temperature 16 °C) and 24 h after the withdrawal of hypobiotic affecting factors (body temperature 37 °C).

Mitochondria were isolated from heart and liver tissues by differential centrifugation, and fraction of the inner mitochondrial membranes (IMM) was sedimented by subsequent centrifugation after freeze-thawing procedure according to standard method [10]. The purity of IMM was assayed via marker enzyme analysis. Lipid extraction from the suspension of IMM was done using the Folch method [11]. Hydrolysis and methylation of lipid fatty acids (FAs) were performed according to the method described in [12]. Gas chromatographic analysis of FAs methyl esters was conducted on the gas chromatograph Trace GC Ultra (USA) with flame ionization detector. Experimental conditions were: column temperature 140-240 °C, detector temperature 260 °C, duration of analysis 65 min. FAs were identified using a standard sample Supelco 37 Component FAME Mix. Quantitative evaluation of FAs spectrum was performed by the method of peak area normalization of FAs methylated derivatives. Their content percentage was calculated.

In the spectrum of lipid fatty acid in IMM the following FAs were identified: myristic C14:0, pentadekanoic C15:0, palmitic C16:0, palmitoleic C16:1, heptadecanoic C17:0, heptadecenoic C17:1, stearic C18:0, oleic C18:1, linoleic C18:2, linolenoic C18:3, gadoleic C20:1, eicosadienoic C20:2, arachidonic C20:4, eicosenic C21:0, docosahexaenoic C22:6.

Statistical analysis of the data was performed in accordance with generally accepted variation statistics methods. The significance of the differences between two groups was evaluated using the Student's *t*-test ($P < 0.05$).

## Results and Discussion

Using the highly sensitive gas chromatography method, we found and quantitatively identified 15 FAs in IMM of cardiomyocytes and 16 FAs in IMM of hepatocytes in intact rats. SFAs are represented mostly by palmitic and stearic acids; lauryl and pentadekanoic acids are in small amount. UFAs are heterogeneous. Particularly, oleic and palmitoleic acids have one saturated bond each. Linolenic, arachidonic and docosahexaenoic acids are polyunsaturated. Among UFAs, polyenoic acids predominate. The total level of UFAs is significantly higher than total level of SFAs (saturation ratios for mitochondrial inner membrane of cardiomyocytes and hepatocytes are 0.74 and 0.66, respectively) (Table 1, 2).

Animals staying in hypoxic-hypercapnic environment with reduced body temperature (artificial hibernation) leads to diverse redistribution of content of SFAs and UFAs in IMM of studied tissues. The SFAs content in IMM of cardiomyocytes is mainly reduced, in particular, palmitic acid by 23.3% compared with the control. This can explain the deficit of energy substrate in cells during hibernation and accumulation of anaerobic glycolysis products. At the same time, the heptadecanoic acid content increases (by 30.1% in comparison with the control). Multidirectional changes in UFAs are also observed. Moreover, the total content of UFAs increases and the total content of SFAs decreases (saturation ratio is 0.65 against 0.74 in control) (Table 1).

The content of monoenoic UFAs decreased significantly ($4.93 \pm 0.11$ against $7.47 \pm 0.22$% in control) mainly due to the lower content of oleic acid ($4.31 \pm 0.03$ against $7.02 \pm 0.06$% in control, $P < 0.05$). At the same time, palmitoleic acid content

increases significantly (by 48% in comparison with the control). We observed the effect of the reduction of the intensity of lipid peroxidation by UFAs due to the neutralization of reactive oxygen species (ROS) [13]. Thus, oleic acid is an endogenous ROS scavenger (as a result, its pool can decrease drastically, as shown in our research) and palmitoleic acid demonstrates cytoprotective action [14].

In this regard, the revealed redistribution of these FAs in IMM of cardiomyocytes possibly indicates their involvement in the protective mechanisms against oxidative stress during hibernation. There were no significant changes in the content of essential FAs such as linoleic and linolenic, which are the most susceptible to oxidation.

The increase in the content of the functionally important FAs was: arachidonic acid (19.93 ± 0.43 against 16.30 ± 0.23% in control, $P < 0.05$) and docosahexaenoic acid (13.09 ± 0.41 against 10.79 ± 0.31% in control, $P < 0.05$). This is associated with the increase of polyenoic UFAs (Table 1). Arachidonic acid (ω-6 polyenoic UFAs), being a part of phospholipids of cell membranes, interacts with protein complexes, affecting the functioning of receptors, transport and signaling systems [15]. One of the mechanisms of action of docosahexaenoic (ω-3 polyenoic UFAs) is also associated with the modification of phospholipid fatty acid composition of cell membranes of cardiomyocytes that affects ion channels and exchangers [16].

The FAs content was not restored to the control level after the withdrawal of the affecting factors (in 24 h). Especially it refers to monoenoic UFAs whose content significantly decreased (3.70 ± 0.11 against 7.67 ± 0.22% in control, $P < 0.05$), mainly due to oleic acid (3.10 ± 0.02 against 7.02 ± 0.06 % in control $P < 0.05$). The total content of UFAs remained also increased, while the saturation ratio was 0.70 against 0.74 in the control (Table 1).

*Table 1. The content of fatty acids (FAs) of inner mitochondrial membrane lipids of rat cardiomyocytes in artificial hypobiosys (HB) and 24 h after it withdrawal (HB24) (M ± m, n = 5)*

| FAs, % | Control | HB | HB24 |
|---|---|---|---|
| C12:0 | 0.13 ± 0.02 | 0.12 ± 0.01 | 0.14 ± 0.01 |
| C14:0 | 0.60 ± 0.02 | 0.22 ± 0.02* | 0.28 ± 0.02* |
| C15:0 | 0.12 ± 0.01 | 0.11 ± 0.01 | 0.10 ± 0.01 |
| C16:0 | 16.80 ± 0.41 | 12.89 ± 0.31* | 12.97 ± 0.23* |
| C16:1 | 0.23 ± 0.02 | 0.34 ± 0.02* | 0.31 ± 0.01* |
| C17:0 | 0.36 ± 0.02 | 0.47 ± 0.02* | 0.49 ± 0.03* |
| C17:1 | 0.23 ± 0.02 | 0.28 ± 0.03 | 0.29 ± 0.03* |
| C18:0 | 24.20 ± 0.53 | 25.32 ± 0.32 | 25.86 ± 0.41 |
| C18:1ω9 | 7.03 ± 0.06 | 4.32 ± 0.03* | 3.11 ± 0.03* |
| C:18:2ω6 | 22.63 ± 0.33 | 22.22 ± 0.52 | 21.60 ± 0.31 |
| C18:3ω3 | 0.13 ± 0.01 | 0.15 ± 0.01 | 0.14 ± 0.01 |
| C20:2ω6 | 0.17 ± 0.01 | 0.34 ± 0.02* | 0.30 ± 0.01* |
| C20:4ω6 | 16.30 ± 0.23 | 19.93 ± 0.43* | 19.55 ± 0.52* |
| C21:0 | 0.20 ± 0.01 | 0.21 ± 0.02 | 0.25 ± 0.02 |
| C22:6ω3 | 10.79 ± 0.31 | 13.09 ± 0.41* | 14.36 ± 0.33* |
| ΣSFAs | 42.41 ± 0.41 | 39.34 ± 0.32 | 40.09 ± 0.42 |
| ΣUFAs | 57.59 ± 0.52 | 60.66 ± 0.60 | 59.91 ± 0.62 |
| SFK/UFK | 0.74 | 0.65 | 0.70 |
| Σ monoenoic UFAs | 7.47 ± 0.22 | 4.93 ± 0.11* | 3.70 ± 0.12* |
| Σ polyenoic UFAs | 50.12 ± 0.31 | 55.73 ± 0.42 | 56.21 ± 0.52 |

Note: Here and in Table 2 data are represented as mass part of individual fatty acid, % of total FAs content. SFAs – saturated fatty acids UFAs – unsaturated fatty acids. *$P < 0.05$ vs control

Thus, during artificial hibernation, the IMM of cardiomyocytes is characterized by diverse redistribution of SFAs and UFAs. In addition, 24-h period after withdrawal of hypobiotic factors is not sufficient for restoration of the FAs content, as it was previously shown with regard to IMM lipid composition [17].

During artificial hibernation, the total content of SFAs in IMM of hepatocytes increased (46.07 ± 0.32 against 39.66 ± 0.32 in control, $P < 0.05$). In particular, the content of palmitic and stearic acids increased by 13.7 and 18.6%, respectively compared with the control. The content of minor SFAs such as lauryl, myristic, heptadecanoic acids increased by 80.0, 90.0 and 20.6% respectively, compared with the control values (Table 2). The ratio of saturated/unsaturated FAs increased (0.86 against 0.66 in control). The regulatory role of SFAs in the membrane should be taken into account.

Specifically, palmitic acid alters mitochondrial permeability due to the ability to induce the opening of $Ca^{2+}$-dependent nonselective pores in lipid membrane of hepatocyte mitochondria [18], which can affect the energetic function of mitochondria during hibernation.

The total content of UFAs in IMM of hepatocytes is reduced mainly due to monoenoic acids (6.21 ± 0.20 against 8.79 ± 0.23 in control $P < 0.05$), including oleic (5.06 ± 0.31 against 8.05 ± 0.31% in control $P < 0.05$), but the palmitoleic acid content increases (0.36 ± 0.01 against 0.64 ± 0.03% in control $P < 0.05$). As stated above, this may be related to the protection of inner membrane mitochondria against oxidation during hibernation. Values for the decrease in the linoleic and linolenic acids content by 37.0 and 48.0%, respectively coincide with the increase of arachidonic acid (precursor of which is linoleic acid) and docosahexaenoic acid by 15.4 and 29.1%, respectively, as compared with control (Table 2), taking into account that the majority of FAs conversions occurs in hepatocytes.

*Table 2. The content of fatty acids (FAs) of inner mitochondrial membrane lipids of rat hepatocytes in artificial hypobiosys (HB) and 24 h after it withdrawal (HB24) (M ± m, n = 6)*

| FAs, % | Control | HB | HB24 |
|---|---|---|---|
| C12:0 | 0.05 ± 0.01 | 0.09 ± 0.02* | 0.07 ± 0.01 |
| C14:0 | 0.21 ± 0.02 | 0.40 ± 0.03* | 0.28 ± 0.02* |
| C15:0 | 0.14 ± 0.01 | 0.17 ± 0.01 | 0.17 ± 0.01 |
| C16:0 | 22.92 ± 0.32 | 26.05 ± 0.35* | 24.10 ± 0.31 |
| C16:1 | 0.36 ± 0.02 | 0.64 ± 0.04* | 0.50 ± 0.03* |
| C17:0 | 0.34 ± 0.02 | 0.41 ± 0.03* | 0.42 ± 0.03* |
| C17:1 | 0.16 ± 0.01 | 0.25 ± 0.01* | 0.20 ± 0.02 |
| C18:0 | 15.64 ± 0.51 | 18.55 ± 0.60* | 18.07 ± 0.71* |
| C18:1ω9 | 8.05 ± 0.31 | 5.06 ± 0.32* | 3.83 ± 0.12* |
| C:18:2ω6 | 24.59 ± 0.77 | 15.54 ± 0.53* | 14.98 ± 0.41* |
| C18:3ω3 | 0.27 ± 0.02 | 0.14 ± 0.01* | 0.14 ± 0.01* |
| C20:1ω9 | 0.22 ± 0.01 | 0.26 ± 0.01* | 0.25 ± 0.01* |
| C20:2ω6 | 0.27 ± 0.01 | 0.25 ± 0.02 | 0.30 ± 0.02 |
| C20:4ω6 | 16.86 ± 0.66 | 19.45 ± 0.72* | 23.14 ± 0.31* |
| C21:0 | 0.36 ± 0.22 | 0.40 ± 0.31 | 0.45 ± 0.21* |
| C22:6ω3 | 9.56 ± 0.42 | 12.34 ± 0.52* | 13.10 ± 0.61* |
| ΣSFAs | 39.66 ± 0.32 | 46.07 ± 0.32* | 43.56 ± 0.44 |
| ΣUFAs | 60.34 ± 0.52 | 53.66 ± 0.41* | 56.44 ± 0.42 |
| SFK/UFK | 0.66 | 0.86 | 0.77 |
| Σ monoenoic UFAs | 8.79 ± 0.23 | 6.21 ± 0.20* | 4.78 ± 0.12* |
| Σ polyenoic UFAs | 51.55 ± 0.62 | 47.45 ± 0.41 | 51.66 ± 0.53 |

The revealed modification of mitochondrial membrane FAs levels indicates the formation of protective - adaptive reactions during artificial hibernation. 24 h after removing the factors of hibernation, there was no restoration of fatty acid content of IMM of hepatocytes to the control level.

Thus, the rats' stay under the conditions of artificially induced hypobiotic state results in significant redistribution of FAs content in IMM of cardiomyocytes and hepatocytes that is caused by structural and functional specificity of the organs. It is well known that liquid-crystalline state of lipids in biological membranes not only supports the essential membrane permeability, but also creates environment for functionally optimal conformational changes of membrane-bound enzyme molecules [19]. The important role of lipids in organisms' adaptation to extreme external factors is the regulation of membrane viscosity, that depends on the chain length and degree of saturation of the FAs of the membrane phospholipids, phospholipids/cholesterol ratio etc. Diverse redistribution of individual FAs content in IMM was accompanied by an increase in the degree of saturation of the FAs of membrane lipids in hepatocytes and insignificant decrease in that in cardiomyocytes. Similar effect was observed in our previous research of the IMM lipid content of hepatocytes and cardiomiocytes: redistribution in the content of individual phospholipids, and increase in total cholesterol and phospholipid levels during hibernation did not result in drastic change of ratio between the individual lipid fractions [17].

Furthermore, the method of fluorescent probes helped to mark modification of IMM structural and dynamic state in cardiomyocytes and hepatocytes during hibernation by integrative parameters, which characterize the membrane surface area, structural orderliness of the lipid components and the protein-lipid interactions in the membrane. Decrease in microviscosity of lipid component and increase in conformational mobility of the membrane-bound protein molecules are inherent for IMM of cardiomyocytes. At the same time the increase in microviscosity and conformational rigidity of the membrane proteins are characteristic for IMM of hepatocytes [20].

The obtained results indicate that in hypothermia development under hypoxic-hypercapnic influence, the IMM reorganizations are specific for cardiomyocytes and hepatocytes, and are likely to have compensatory nature, directed at maintaining of functional activity of mitochondrial membranes, especially of the respiratory chain under new conditions of existence, as it was shown previously [9, 21].

Regarding the influence of FAs on the processes of oxidative phosphorylation of mitochondrial respiratory chain, different mechanisms are considered. The increase in the UFAs content leads to the formation of continuous regions with unsaturated bonds and different charge in membrane monolayer. As a result, there are areas in the membrane with different ability to accept electron. The significance of this phenomenon is described with regard to adaptation of membranes to ambient temperature [22]. In addition, long-chain FAs are known to be natural oxidative phosphorylation uncouplers in mitochondria. They act as protonophores, causing dissipation of transmembrane potential. In the presence of calcium ions, the formation of nonspecific pores in the mitochondrial membrane (with the involvement of FAs) plays a special role in uncoupling of oxidation and phosphorylation [16]. It was shown that the uncoupling effect during cold stress, acclimatization or exit from the state of hibernation can boost thermogenesis, especially in muscle tissue [4].

Regarding the course of oxidative processes in IMM, modification of functional activity of respiratory chain complexes during hypothermia under the influence of hypoxia-hypercapnia [9, 21] may increase the formation of ROS in the membrane. According to current views, oleic acid is not only a structural component of cell membranes, but also the main endogenous ROS acceptor and has a high rate of ATP oxidation if compared with other of polyenoic UFAs (arachidonic and linoleic). Only after the oxidation of oleic acid, the remaining pool of ROS reacts with other acids, particularly arachidonic, forming conjugated dienes [14].

Increased level of arachidonic acid in IMM can be caused by several events. It can be the increase of its formation in the cytoplasm and intracellular redistribution, as well as disrupture of interaction with the membrane protein complexes due to their modification during hibernation. Polyenoic UFAs are the precursors of biologically active substances [1]. Derivatives of arachidonic ω-6 polyenoic UFAs are a number of thromboxanes, leukotrienes that increase the permeability of the membrane and cause inflammations. Metabolites of ω-3 polyenoic UFAs (prostaglandins, thromboxanes, leukotrienes), which are antiaggregant, anti-inflammatory substances that contribute to the stabilization of membranes [16]. For this reason, it is important to maintain the physiological ratio of ω-3: ω-6 polyenoic UFAs.

Taking into consideration the direct involvement of polyenoic UFAs in regulation of majority of cellular processes, the discovered fact of their redistribution in IMM explains the involvement of these acids in cell regulation of artificial hibernation and the process of exit from this state. Thus, the mechanism of transformation of membrane components created in the course of evolution is one of the factors of preservation of viability in the conditions of body temperature reduction during hypercapnia and hypoxia. Investigation of the role of fatty acids is necessary for understanding the ways of mammalian adaptation to low temperatures, as well as finding ways to support and secure long and safe hibernation.

## ЖИРНОКИСЛОТНИЙ СКЛАД ВНУТРІШНЬОЇ МЕМБРАНИ МІТОХОНДРІЙ КАРДІОМІОЦИТІВ ТА ГЕПАТОЦИТІВ ЩУРІВ ЗА ГІПОКСИ-ГІПЕРКАПНІЧНОГО ВПЛИВУ

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Досліджено вплив гіпокси-гіперкапнічного середовища за гіпотермії (штучний гіпобіоз) на жирнокислотний спектр ліпідів внутрішньої мембрани (ВМ) мітохондрій гепатоцитів та кардіоміоцитів щурів. За гіпобіозу встановлено специфічний для клітинних органел перерозподіл у вмісті жирних кислот ВМ мітохондрій, який для кардіоміоцитів призводить до зниження сумарної кількості насичених жирних кислот (НЖК) та підвищення ненасичених жирних кислот (ННЖК), а для гепатоцитів – до підвищення НЖК та зниження ННЖК. Показано зниження вмісту олеїнової кислоти, зростання вмісту арахідонової та докозагексаєнової кислот, що може обумовлюватись їх участю в регуляторних системах як за гіпобіозу, так і під час виходу із цього стану. Передбачається, що стан штучного гіпобіозу характеризується стрес-реакцією, яка призводить до оптимальної перебудови жирнокислотного складу мембранних ліпідів, направленої на підтримку функціональної активності мітохондрій гепатоцитів і кардіоміоцитів.

Ключові слова: насичені та ненасичені жирні кислоти, внутрішня мембрана мітохондрій, гепатоцити, кардіоміоцити, гіпоксія, гіперкапнія, гіпотермія.

## ЖИРНОКИСЛОТНЫЙ СОСТАВ ВНУТРЕННЕЙ МЕМБРАНЫ МИТОХОНДРИЙ КАРДИОМИОЦИТОВ И ГЕПАТОЦИТОВ КРЫС ПРИ ГИПОКСИ-ГИПЕРКАПНИЧЕСКОМ ВОЗДЕЙСТВИИ

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Исследовано воздействие гипокси-гиперкапнической среды при гипотермии (искусственный гипобиоз) на жирнокислотный спектр липидов внутренней мембраны (ВМ) митохондрий гепатоцитов и кардиомиоцитов крыс. При гипобиозе установлено специфическое для клеточных органелл перераспределение в количестве жирных кислот ВМ митохондрий, приводящее в кардиомиоцитах к снижению суммарного количества насыщенных жирных кислот (НЖК) и увеличению ненасыщенных жирных кислот (ННЖК), а для гепатоцитов – к увеличению НЖК и снижению ННЖК. Показано снижение содержания олеиновой кислоты, повышение – арахидоновой и докозагексаеновой кислот, что, возможно, обусловлено их участием в регулирующих системах как при гипобиозе, так и при выходе из этого состояния. Предполагается, что состояние искусственного гипобиоза характеризуется стресс-реакцией, приводящей к оптимальной перестройке жирнокислотного состава мембранных липидов, направленной на поддержание функциональной активности митохондрий гепатоцитов и кардиомиоцитов.

Ключевые слова: насыщенные и ненасыщенные жирные кислоты, внутренняя мембрана митохондрий, гепатоциты, кардиомиоциты, гипоксия, гиперкапния, гипотермия.

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