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Electron microscopy study of left ventricular cardiomyocytes in adult rats born preterm

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ABSTRACT

BACKGROUND: Preterm birth is a risk factor for the early development of cardiovascular diseases. Thus far, based on the results of clinical studies, the ultrastructural features of cardiomyocytes in adolescents and adults born prematurely can be identified. Thus, experiments aimed at studying the effects of preterm birth on the ultrastructure of cardiomyocytes in the late postnatal period of ontogenesis are relevant.

AIM: To identify the ultrastructural features of left ventricular cardiomyocytes in preterm adult rats.

MATERIALS AND METHODS: The study was conducted on full-term (n=4, pregnancy duration 22 days) and preterm (n=4, pregnancy duration 21 days) male Wistar rats. Preterm labor was induced by mifepristone injection to pregnant rats. Preterm and full-term offspring were removed from the experiment on day 180 of the postnatal period of ontogenesis. Fragments of the left ventricle of the heart of preterm and full-term rats were used for the ultrastructural studies of the cardiomyocytes (electron transmission microscopy). Electron microphotographs of longitudinal sections of contractile cardiomyocytes were used to determine the relative areas of the nucleus, cytoplasm, myofibrils, and mitochondria.

RESULTS: The structure of the cardiomyocytes of preterm and full-term rats on postnatal day 180 was fundamentally similar. However, the relative area of the nuclei of cardiomyocytes in preterm rats was lower (p=0.02), and the relative area of the cytoplasm was higher (p=0.02) than that in full-term animals. Exclusively, in the cytoplasm of preterm rats, perinuclear swelling of the cytoplasm, thinning of myofibrils, and signs of mitochondrial damage, such as destruction of mitochondrial membranes, concentric organization of mitochondrial cristae, and dissociation of mitochondrial clusters, were observed.

CONCLUSION: Preterm birth has chronic negative effects on the ultrastructure of cardiomyocytes. The observed ultrastructural changes lead to the disruption of energy production in the cardiomyocytes in the late postnatal period of ontogenesis of preterm rats.

Keywords: preterm birth; cardiomyocytes; ultrastructure; animal experimentation.

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Электронно-микроскопическое исследование кардиомиоцитов левого желудочка половозрелых крыс, рождённых недоношенными

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АННОТАЦИЯ

Обоснование. Преждевременное рождение является фактором риска раннего развития заболеваний сердечно-сосудистой системы. На сегодняшний день по результатам клинических исследований невозможно составить представление о структурных особенностях кардиомиоцитов подростков и взрослых, рождённых недоношенными. Актуальным в этой связи является экспериментальное исследование влияния преждевременного рождения на ультраструктуру кардиомиоцитов в отдалённом постнатальном периоде онтогенеза.

Цель исследования — выявление ультраструктурных особенностей кардиомиоцитов левого желудочка у недоношенных половозрелых крыс.

Материалы и методы. Исследование проведено на доношенных (*n*=4, продолжительность беременности 22 сут) и недоношенных (*n*=4, продолжительность беременности 21 сут) самцах крыс линии Вистар. Преждевременные роды стимулировали введением беременным крысам мифепристона. Преждевременно рождённое и доношенное потомство выводили из эксперимента на 180-е сутки постнатального периода онтогенеза. Фрагменты левого желудочка сердца недоношенных и доношенных крыс использовали для ультраструктурного исследования кардиомиоцитов (трансмиссионная электронная микроскопия). На электронограммах продольных срезов сократительных кардиомиоцитов определены относительные площади ядра, цитоплазмы, миофибрилл, митохондрий.

Результаты. Строение кардиомиоцитов недоношенных и доношенных крыс на 180-е сутки постнатального периода принципиально схоже. Однако относительная площадь ядер кардиомиоцитов недоношенных крыс ниже (*p*=0,02), а цитоплазмы — выше (*p*=0,02), чем у доношенных животных. Исключительно в цитоплазме недоношенных крыс наблюдаются перинуклеарное набухание цитоплазмы, истончение миофибрилл, а также признаки повреждения митохондрий, такие как деструкция митохондриальных мембран, концентрическая организация крист митохондрий, диссоциация кластеров митохондрий.

Заключение. Преждевременное рождение оказывает пролонгированное негативное влияние на ультраструктуру кардиомиоцитов. Наблюдаемые структурные изменения приводят к нарушению энергопродукции в кардиомиоцитах недоношенных крыс в отдалённом постнатальном периоде онтогенеза.

Ключевые слова: преждевременное рождение; кардиомиоциты; ультраструктура; эксперимент.

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性成熟早产大鼠左心室心肌细胞的电子显微镜研究

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摘要

论证。早产是心血管系统疾病早期发展的危险因素。迄今为止，还无法根据临床研究结果了解早产青少年和成人心肌细胞的结构特征。因此，通过实验研究早产对出生后远期本体发育阶段心肌细胞超微结构的影响具有重要意义。

本研究旨在确定性早熟大鼠左心室心肌细胞的超微结构特征。

材料和方法。该研究在足月（n=4，妊娠22天）和早产（n=4，妊娠21天）雄性Wistar大鼠中进行。对怀孕大鼠施用米非司酮诱发早产。在出生后个体发育的第180天，早产和足月后代被排除在实验之外。利用早产大鼠和早衰大鼠的左心室切片对心肌细胞进行超微结构研究（透射电子显微镜）。细胞核、细胞质、肌纤维和线粒体的相对面积是在收缩心肌细胞纵切面的电子图上确定的。

结果。出生后第180天早产和足月大鼠心肌细胞的结构基本相似。但是，但早产大鼠心肌细胞核相对面积低于足月动物(p=0.02)，而胞质的相对面积比早产动物高（p=0.02）。细胞质核周肿胀、肌纤维变细以及线粒体损伤的迹象，如线粒体膜破坏、线粒体嵴同心组织、线粒体簇解离等，只在早产大鼠的细胞质中观察到。

结论。早产对心肌细胞超微结构有长期的负面影响。观察到的结构变化导致早产大鼠的心肌细胞在出生后的远期能量生成受损。

关键词： 早产；心肌细胞；超微结构；实验。

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BACKGROUND

Prematurity is linked to the early development of cardiovascular diseases [1]. Recent research has aimed to establish the structural basis for functional cardiac alterations in adolescents and adults who were born prematurely. Premature infants (born between 22 and 37 weeks of gestation) exhibit more spherical hearts in adolescence and adulthood [2] than their full-term counterparts. Additionally, their myocardium exhibits more pronounced interstitial fibrosis [3, 4]. However, clinical investigations alone are insufficient to establish an understanding of the histological and ultrastructural features of the myocardium of prematurely born individuals in adolescence and adulthood. Hence, there is a need for additional experimental research focused on this issue.

This study aimed to identify the ultrastructural features of left ventricular cardiomyocytes in prematurely born mature rats.

MATERIALS AND METHODS

Study design

The study was prospective, experimental, single-center, randomized, controlled, and non-blinded.

Eligibility criteria

The investigation was conducted on male Wistar rats that were full-term and 24-hour premature. Based on the duration of intrauterine development, we classified the animals into two groups: full-term and premature, with Wistar rats having a total gestation period of 22 days.

Settings

The study was conducted at the Siberian State Medical University of the Ministry of Health of the Russian Federation. Standard vivarium conditions were implemented to effectively maintain the animals.

Duration of the study

The study was conducted on day 180 of postnatal ontogenesis in Wistar rats to ascertain the long-term effects of prematurity on the structural elements of cardiomyocytes.

Description of medical intervention

The offspring were obtained from mature Wistar male (2 months old, 200 g) and female (3 months old, 200 g) rats. The following morning, a vaginal smear was conducted to confirm coitus after the animals were confined overnight. The first day of pregnancy was determined to be the day on which sperm was detected in the vaginal smear. Pregnant females were randomly divided into those who gave birth naturally and those who were induced to deliver prematurely. Full-term animals were obtained through the natural, non-stimulated births of rats. A single subcutaneous injection of the antiprogestin mifepristone (1 mL, 10 mg/kg body weight, Sigma-Aldrich, USA) was administered on the 20th day of gestation to induce premature labor. The introduction of antiprogestins to pregnant rats led to labor onset within 18–24 hours [5].

Primary outcome of the study

The structural characteristics of cardiomyocytes in premature rats, as determined on day 180 of postnatal ontogenesis, were the primary outcome.

Group analysis

The study was conducted on full-term (n=4, 22 days of gestation) and premature (n=4, 21 days of gestation) sexually mature male Wistar rats. To confirm premature birth, the rats were weighed at the time of birth using an HL-100 laboratory balance (Japan).

Methods of recording outcomes

The rats were euthanized by carbon dioxide asphyxiation on the 180th day of postnatal ontogenesis. Myocardial fragments from the middle third of the lateral wall of the left ventricle were fixed in 4% paraformaldehyde (Serva, Germany) for a day, then in 1% osmium tetroxide (SPI, USA) for 3 hours. The fragments are then embedded in a mixture of Epon 812, Araldite 502, and DDSA resins (SPI, USA). Sections of 80 nm thickness were obtained using a Leica EM UC 7 ultramicrotome (Leica, Austria) and contrasted with uranyl acetate and lead citrate. The ultrastructural analysis was performed using the JEM-1400 transmission electron microscope (JEOL, Japan). The morphometric analysis of the obtained images was conducted using the ImageJ 1.48 software (NIH, USA). Electronograms of longitudinal sections of contractile cardiomyocytes were used to determine the relative areas of the nucleus, cytoplasm, myofibrils, and mitochondria. Morphometric analysis was conducted on a minimum of five cardiomyocytes from each sample of all animals included in the investigation.

Ethical review

The study was conducted in accordance with the Federal Law of the Russian Federation "On the Protection of Animals from Cruel Treatment" dated January 1, 1997. The research protocol has been approved by the local ethics committee of the Siberian State Medical University of the Ministry of Health of Russia (No. 8475/1, dated November 30, 2020).

Statistical analysis

The quantitative indicators were analyzed using the SPSS 16.0 program (IBM, USA). Descriptive statistics data are presented as medians and quartiles (Me [Q1; Q3]). The normality of the distribution was verified using the Shapiro-Wilk test. We used the Mann-Whitney criterion to

identify differences between groups due to the non-normal distribution. The statistical significance of differences was established at a level of $p < 0.05$.

RESULTS

Study participants

At the time of birth, the weight of premature male rats was 4.3 g (4.1; 4.6), which is significantly (p=0.000) lower than the weight of full-term male rats at 6.0 g (5.7; 6.2).

Main study results

The ultrastructural structure of cardiomyocytes in premature and full-term rats on day 180 of the postnatal period was detected to be comparable (Fig. 1).

The myocardium was composed of cardiomyocytes with two oval-shaped nuclei that were centrally located and dominated by euchromatin. However, the relative area of cardiomyocyte nuclei in premature rats was significantly lower, while the cytoplasm was higher than that of full-term animals (Table 1). The observed differences were linked to the development of perinuclear swelling of the cytoplasm in the cardiomyocytes of premature rats (Fig. 1, *b*).

The myofibril bundles in the cardiomyocytes of premature rats are oriented appropriately. The relative area of myofibrils does not differ from that in full-term rats (see Table 1). Myofibril thinning was observed in certain cardiomyocytes of premature rats. (Fig. 2, *a*).

Numerous mitochondria were observed to exhibit subsarcolemmal, intermyofibrillar, and perinuclear localization in the cardiomyocytes of premature rats, as observed in full-term animals. On day 180 of postnatal ontogenesis, we found no differences in the relative area of cardiomyocyte mitochondria between premature and full-term rats (Table 1). However, cardiomyocytes of premature rats exhibited mitochondria with damage to the

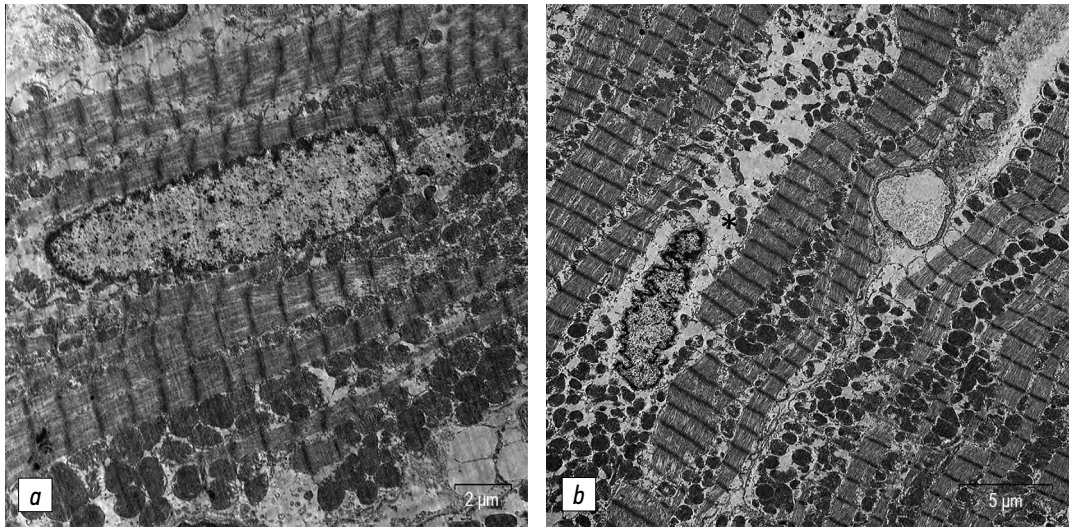

Fig. 1. Myocardium of the left ventricle of term (*a*) and preterm (*b*) male rats, 180 days of postnatal ontogenesis. Uranyl acetate and lead citrate, ×20 000 (*a*), ×12 000 (*b*). Perinuclear swelling of the cytoplasm (*) of a cardiomyocyte of a preterm animal.
Рис. 1. Миокард левого желудочка доношенных (*a*) и недоношенных (*b*) самцов крыс на 180-е сутки постнатального онтогенеза. Окрашивание уранил ацетатом и цитратом свинца, ×20 000 (*a*), ×12 000 (*b*). Звёздочкой (*) отмечено перинуклеарное набухание цитоплазмы кардиомиоцита у недоношенного животного.

Table 1. Relative area of rat cardiomyocytes structural elements
Таблица 1. Относительная площадь структурных элементов кардиомиоцитов крыс

Group	Relative area of structures, Me [Q1; Q3], %			
	nucleus	cytoplasm	myofibril	mitochondria
Term rats	10,5 [8,3; 11,8]	89,5 [88,3; 91,8]	37,5 [33,3; 42,5]	19,5 [18,0; 21,8]
1 day preterm rats	6,0 [4,0; 7,8]* p=0,02	94,0 [92,3; 96,0]* p=0,02	36,5 [34,0; 40,5]	18,0 [16,3; 20,0]

* statistically significant differences from the index of term rats.
* статистически значимые отличия от показателя доношенных крыс.

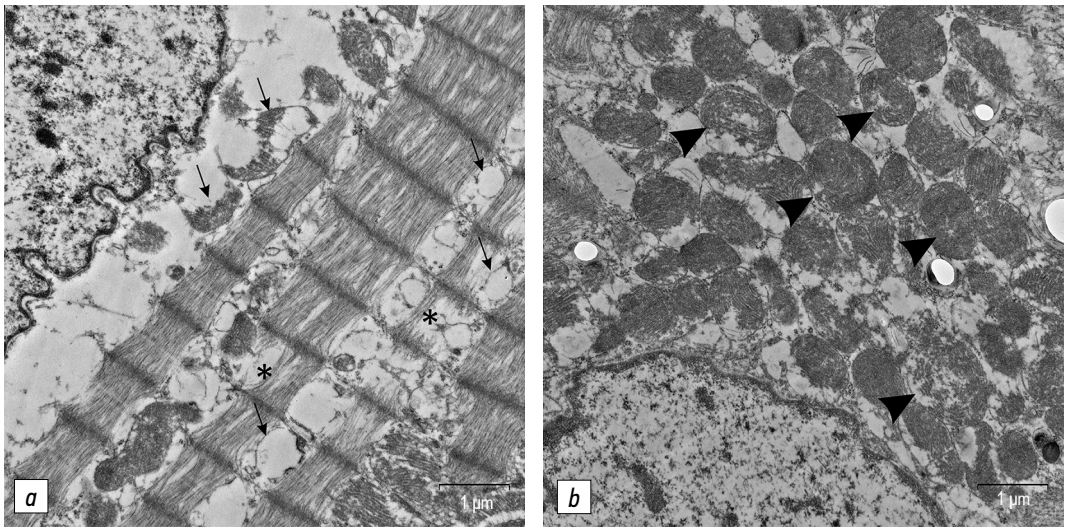

Fig. 2. A fragment of the cytoplasm of a cardiomyocyte from preterm male rats (*a*, *b*) 180 days of postnatal ontogenesis. Uranyl acetate and lead citrate, ×25 000 (*a*, *b*). Mitochondrial damage (arrows). Mitochondria with concentric cristae (arrowshead). Thinning of myofibrils (*).

Рис. 2. Фрагмент цитоплазмы кардиомиоцита недоношенных самцов крыс (*a*, *b*) на 180-е сутки постнатального онтогенеза. Окрашивание уранил ацетатом и цитратом свинца, ×25 000 (*a*, *b*). Повреждение митохондрий обозначено стрелками; головки стрелок указывают на митохондрии с концентрическими кристами. Звёздочками (*) отмечено истончение миофибрилл.

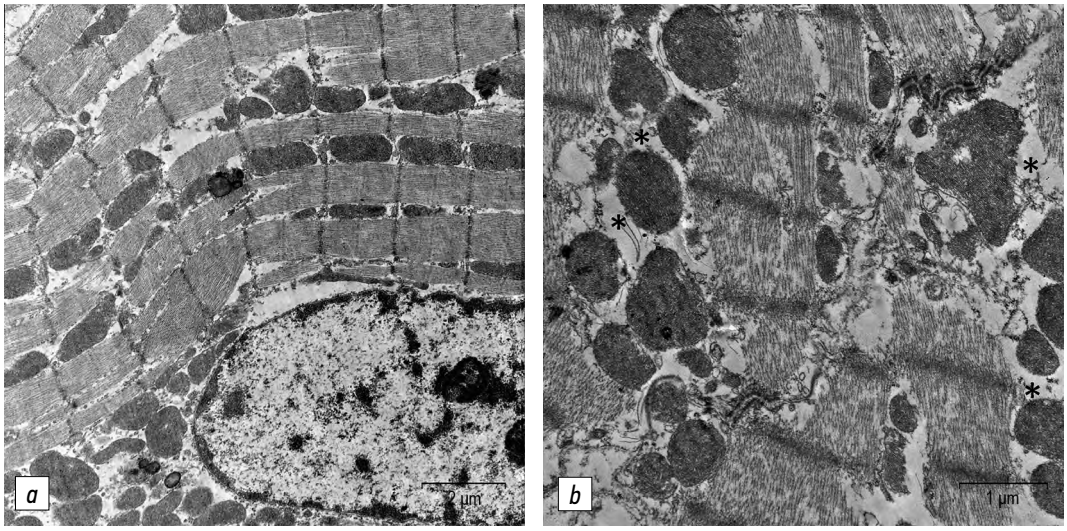

Fig. 3. A fragment of the cytoplasm of a cardiomyocyte from term (*a*) and preterm (*b*) male rats, 180 days of postnatal ontogenesis. Uranyl acetate and lead citrate, ×18 000 (*a*), ×30 000 (*b*). Dissociation of clasters of mitochondria in the cytoplasm of a cardiomyocyte of a preterm animal (*).

Рис. 3. Фрагмент цитоплазмы кардиомиоцита доношенных (*a*) и недоношенных (*b*) самцов крыс на 180-е сутки постнатального онтогенеза. Окрашивание уранил ацетатом и цитратом свинца, ×18 000 (*a*), ×30 000 (*b*). Звёздочками (*) отмечена диссоциация кластеров митохондрий в цитоплазме кардиомиоцита недоношенного животного.

inner or both membranes (see Fig. 2, *a*). Alterations were detected in mitochondria regardless of their location within the cardiomyocyte. Mitochondria with concentric cristae were found exclusively in the cardiomyocytes of premature rats (see Fig. 2, *b*). The cardiomyocytes of premature rats exhibited a scattered arrangement of mitochondria in the cytoplasm, while the mitochondria were arranged in clusters in the cells of full-term animals (Fig. 3).

On day 180 of postnatal ontogenesis, cardiomyocytes did not exhibit any ultrastructural changes in the structure of the sarcoplasmic reticulum and T-tubules, as well as intercellular contacts.

DISCUSSION

Summary of the main study result

Cardiomyocytes did not exhibit any ultrastructural alterations in the structure of the sarcoplasmic reticulum and T-tubules, as well as intercellular contacts, on day 180 of postnatal ontogenesis.

Discussion of the main study results

To date, ultrastructural myocardial analysis has been conducted exclusively on premature infants who died in the neonatal period [6, 7], whereas the long-term effects of premature birth on the structural elements of the human cardiomyocyte have not been described. Compared to full-term infants, premature infants exhibited a lower degree of cardiomyocyte differentiation as well as signs of cardiomyocyte damage, including perinuclear edema and mitochondrial membrane destruction [6, 7]. In the remote postnatal period of ontogenesis, it would be intriguing to ascertain whether premature birth influences the ultrastructure of cardiomyocytes.

To accomplish this, individual experimental tests examining the cardiomyocyte ultrastructure were performed in animals that were modeled to simulate prematurity. Researchers adopted a model that maintained full-term rats during the neonatal period under hyperoxic conditions, to establish the prematurity model [8]. This study was conducted on male rats born 24 hours prematurely, since we hypothesized that the phenomenon of prematurity primarily involves the birth of an organism with structurally and functionally immature organs, which cannot be solely attributed to the effects of hyperoxia.

We identified structural and functional alterations in the cardiomyocytes of premature animals in the late postnatal period of ontogenesis. In premature animals, the cardiomyocytes exhibit mitochondrial membrane destruction, dissociation of mitochondrial clusters, and concentric organization of mitochondrial cristae. These changes lead to a disruption of energy production in cells, the decoupling of oxidation and phosphorylation processes, as well as the production of reactive oxygen species. In the late postnatal period, K.N. Goss et al. [8] demonstrated a decrease in the activity of superoxide dismutase 1 and 2 in rat myocardium modeled for prematurity (neonatal hyperoxia). Increased generation of reactive oxygen species, accompanied by decreased activity of antioxidant enzymes, may be the cause of pronounced oxidative stress.

The underlying causes for the appearance of mitochondria with a concentric arrangement of cristae are incompletely understood. However, it has been documented that such a spatial organization of cristae occurs when the mitochondrial or nuclear genome is damaged, including by oxidative stress [9, 10]. The spatial organization of cristae is facilitated by inner mitochondrial membrane proteins and phospholipids. Genomic damage may lead to dysfunction of the structural proteins and enzymes responsible for the production of mitochondrial membrane phospholipids [11]. The mitochondrial genome in cardiomyocytes in the late postnatal period of ontogenesis (1 year) has been demonstrated to be significantly damaged in a prematurity model that involves maintaining full-term rats in hyperoxic conditions during the neonatal period [8]. Damage to the mitochondrial membrane phospholipoids, in particular cardiolipin, which plays a critical role in the spatial organization of cristae, may be caused by the direct action of reactive oxygen species [12, 13]. Furthermore, hypoxia can disrupt the production of cardiolipin [14]. A disruption in the quantity or structure of cardiolipin can lead to the formation of concentric cristae within the mitochondria [11]. The concentric organization of mitochondrial cristae, according to A. Vincent et al. [10], causes a decline in their energy production efficiency.

In normal cardiomyocytes, mitochondria organize into structurally functional clusters. The coordinated functioning of mitochondria within a cluster is due to the presence of specific protein inter-mitochondrial contacts [15]. The mitochondria in the cardiomyocytes of premature rats are dispersed and do not establish inter-mitochondrial contacts. Thus, it can be concluded that there is functional discoordination among cardiomyocyte mitochondria in premature animals. Mitochondrial damage is one of the factors in the dissociation of mitochondria from the cluster. Additionally, it is recognized that the cluster does not encompass newly formed and dividing mitochondria [15].

The myofibril thinning and swelling of the perinuclear cytoplasm in the cardiomyocytes of premature animals may be a result of both energy deficiency and damage caused by reactive oxygen species.

Therefore, in the late postnatal period in prematurely born rats as well as in premature newborns [6, 7], swelling of the cytoplasm and mitochondrial damage are observed in cardiomyocytes. It can thus be inferred that premature birth leads to prolonged stereotypical disturbances in the structural elements of cardiomyocytes. Notably, individuals who are born prematurely exhibit signs of impaired energy metabolism, even in the late postnatal period. At the age of 25–26, monocytes of individuals born prematurely exhibited an increase in mitochondrial oxidative activity, but with decreased efficiency of adenosine triphosphate production [16].

Study limitations

The study's limitation is the small sample size. In the future, additional studies comparing the observed structural disorders with the results of functional studies that have examined the activity and efficiency of oxidative phosphorylation in the mitochondria of cardiomyocytes in premature rats are planned.

CONCLUSIONS

Premature birth has a prolonged adverse effect on cardiomyocyte ultrastructure. The resulting structural alterations disrupt energy production in the cardiomyocytes of premature rats in the late postnatal period of ontogenesis.

ADDITIONAL INFORMATION

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

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. V.V. Ivanova — experimental procedures, collection and analysis of literary sources, writing the text and editing the article; I.V. Milto — experimental procedures, editing the article.
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