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ULTRASTRUCTURAL CHANGES IN THE RESPIRATORY ZONE OF THE LUNGS IN THE LATE STAGES OF EXPERIMENTAL DIABETES MELLITUS

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УЛЬТРАСТРУКТУРНІ ЗМІНИ В РЕСПІРАТОРНІЙ ЗОНІ ЛЕГЕНЬ НА ПІЗНИХ СТАДІЯХ ЕКСПЕРИМЕНТАЛЬНОГО ЦУКРОВОГО ДІАБЕТУ

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Summary/Резюме

The purpose of the study is to evaluate the dynamics of changes in the components of the respiratory part of the lungs in streptozotocin-induced diabetes. The experiments were performed on 68 white male Wistar rats weighing 180-220 g. The animals were divided into three groups: 1 — intact (*n* = 10); 2 — control (*n* = 30); 3 — experimental (*n* = 28) with a model of diabetes mellitus, which was reproduced by streptozotocin i.p. injection ("Sigma" (USA), diluted in 0.1 M citrate buffer (pH = 4.5) at a rate of 60 mg/kg body weight. The control group of animals received an intraperitoneal injection with an equivalent dose of 0.1 M citrate buffer solution (pH = 4.5). Pulmonary tissue collection for electron microscopic examination was performed under thiopental anesthesia 56, 70 and 84 days after streptozotocin injection. Pieces of lung tissue were fixed in 2.5 % glutaraldehyde solution, followed by fixation in 1 % osmium tetroxide solution. After dehydration, the material was poured into epon-araldite. Sections obtained on an ultramicrotome "Tesla BS-490" were studied in an electron microscope «PEM-125K». All studies were performed under sodium thiopental anesthesia at the rate of 60 mg/kg of body weight. Our research showed that 56, 70 and 84 days after the modeling of streptozotocin-induced diabetes changes of a dystrophic-destructive nature were noted in alveolocytes of types I and II, and endotheliocytes of hemocapillaries. At the same time, cells with increased functional activity were determined in the components of the respiratory part of the lungs. Streptozotocin-induced diabetes leads to severe violations of the ultrastructural organization of components of the respiratory part of the lungs. The nature and severity of structural changes in type I, II alveolocytes, and endotheliocytes of hemocapillaries depend on the duration of diabetes.

Key words: *streptozotocin-induced diabetes, lungs, respiratory part, pathophysiologic mechanisms*

Метою дослідження є оцінка динаміки змін компонентів дихальної частини легень при стрептозотоцин-індукованому діабеті. Експерименти проводили на 68 білих самцях щурів лінії Вістар вагою 180-220 г. Тварин розділили на три групи: 1 — інтактна (*n* = 10); 2 — контрольна (*n* = 30); 3 — експериментальна (*n* = 28) з моделлю цукрового діабету, яку відтворювали стрептозотоцином внутрішньоочеревинно. ін'єкцію («Sigma» (США), розведену в 0,1 М цитратному буфері (pH = 4,5) з розрахунку 60 мг/кг маси тіла. Контрольна група тварин отримувала внутрішньочеревну ін'єкцію з еквівалентною дозою 0,1 М цитратного буферного розчину (pH = 4,5). Забір тканини легень для електронно-мікроскопічного дослідження проводили під тіопенталовим наркозом через 56, 70 та 84 дні після ін'єкції стрептозотоцину. Шматочки тканини легень фіксували у 2,5 % розчині глутаральдегіду, а потім фіксували у 1 % розчині чотириокису осмію. Після зневоднення матеріал заливали в епон-араль-

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дит. Зрізи, отримані на ультрамікротомі «Tesla BS-490», досліджували на електронному мікроскопі «PEM-125K». Всі дослідження проводили під тіопенталовим наркозом з розрахунку 60 мг/кг маси тіла. Наші дослідження показали, що через 56, 70 та 84 дні після моделювання стрептозотоцин-індукованого діабету відзначалися зміни дистрофічно-деструктивного характеру в альвеолоцитах I та II типів, а також ендотеліоцитах гемокапілярів. Водночас у компонентах дихальної частини легень визначалися клітини з підвищеною функціональною активністю. Стрептозотоцин-індукований діабет призводить до тяжких порушень ультраструктурної організації компонентів дихальної частини легень. Характер та тяжкість структурних змін в альвеолоцитах I, II типів та ендотеліоцитах гемокапілярів залежать від тривалості діабету.

Ключові слова: *стрептозотоцин-індукований діабет, легені, дихальна частина, патофізіологічні механізми.*

Nowadays, diabetes mellitus (DM) is one of the major problems of modern medicine and is among the most common endocrine diseases. According to estimates from the International Diabetes Federation (IDF), nearly 425 million people had DM in 2017, and the number is expected to rise to 629 million by 2045 [6, 7, 9, 10].

Diabetes mellitus is a metabolic disorder with a debilitating impact on many organs [8, 14, 16]. Currently, an increasing number of reports in the literature describe damage to the respiratory portion of the lungs in DM [1, 3, 5, 13].

The purpose of the study is to evaluate the dynamics of changes in the components of the respiratory part of the lungs in streptozotocin-induced diabetes.

Materials and methods

The experiments were performed on 68 white male Wistar rats weighing 180-220 g. The animals were divided into three groups: 1 — intact (n = 10); 2 — control (n = 30); 3 — experimental (n = 28) with a model of diabetes mellitus, which was reproduced by intraperitoneal injection of streptozotocin company “Sigma” (USA), diluted in 0.1 M citrate buffer with pH 4.5, at a rate of 60 mg/kg body weight. The control group of animals received an intraperitoneal injection with an equivalent dose of 0.1 M citrate buffer solution with a pH of 4.5.

Pulmonary tissue collection for electron microscopic examination was performed under thiopental anesthesia 56, 70 and 84 days after streptozotocin injection. Pieces of lung tissue were fixed in 2.5 % glutaraldehyde solution, followed by fixation in 1 % osmium tetroxide solution. After dehydration, the material was poured into epon-araldite. Sections obtained on an ultramicrotome “Tesla BS-490” were studied in an electron microscope «PEM-125K». All studies were performed under sodium thiopental anesthesia at the rate of 60 mg/kg of body weight.

Animal husbandry and research were conducted in accordance with the provisions of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (Strasbourg, 1986), the Law of Ukraine on the “Protection of Animals from Cruelty” (2006) and the “General Ethical Principles of Experiments on animals” approved by the Fifth National Congress on Bioethics (Kiev, 2013).

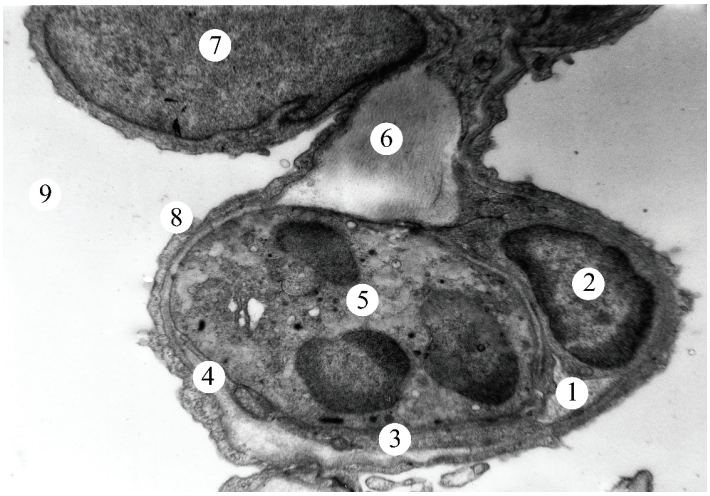

Fig. 1. Ultrastructural organization of the respiratory part of the lungs 56 days after the start of the experiment. Electronic microphotography x6400
Marking: 1 — lumen of the hemocapillary; 2 — nucleus of endotheliocyte 3 — peripheral part of endotheliocyte; 4 — basal membrane; 5 — leukocyte; 6 — interstitial tissue; 7 — nucleus of alveolocyte type I; 8 — peripheral part of alveolocyte type I; 9 — lumen of alveoli.

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Results and their discussion

The submicroscopic analysis showed that 56 days after the start of the experiment, the nuclei of some type I alveolocytes (A-I), type II alveolocytes (A-II), and hemocapillary endothelial cells contained matrix with low electron-optical density (Fig. 1).

Chromatin granules in many cases were located along the inner surface of the nuclear envelope or grouped into separate clusters. The perinuclear space was expanded. Mitochondria were enlarged in volume with only a few cristae. The Golgi apparatus (GA) was represented by dilated cisternae and vacuoles.

The tubules of the rough endoplasmic reticulum (RER) were vacuolized with a reduced number of ribosomes on their membranes. In the lumens of hemocapillaries, adhesion and aggregation of leukocytes and platelets were observed, as well as erythrocyte sludging. The basal membrane was thickened with indistinct contours.

In addition, pronounced interstitial tissue edema was noted. Severe disturbances in the ultrastructural organization of the components of the respiratory portion of the lungs were detected 70–84 days into the experiment. In A-I, A-II, and hemocapillary endothelial cells, the development of intracellular edema with disruption of organelle structure was observed.

The mitochondria of these cells had matrix of low electron-optical density and disoriented, sparse cristae. In some cases, complete lysis of the cristae was detected. The cisternae of the GA and the RER tubules were dilated. Fragmentation of RER membranes was also observed. In A-II cells, some lamellar bodies were partially filled with phospholipid material and fragmented lamellae. Thrombo-leukocytic aggregates were present in hemocapillaries. In certain microvessels, disruption of the integrity of the luminal plasmalemma was observed.

Our findings indicate the presence of dystrophic and destructive changes in the components of the respiratory portion of the lungs at late stages of experimental diabetes mellitus. Similar changes have also been reported by other researchers studying the submicroscopic structure of the respiratory portion of the lungs under various endogenous factors [2, 4, 11, 12, 15].

Conclusion

Streptozotocin-induced diabetes leads to severe violations of the ultrastructural organization of components of the respiratory part of the lungs. The nature and severity of structural changes in type I, II alveolocytes, and endotheliocytes of hemocapillaries depend on the duration of diabetes.

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ПАТОФІЗІОЛОГІЧНІ МЕХАНІЗМИ РАДІАЦІЙНО-ІНДУКОВАНОЇ МІТОХОНДРІАЛЬНОЇ ДИСФУНКЦІЇ У НАЩАДКІВ ОПРОМІНЕНИХ ТВАРИН

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PATHOPHYSIOLOGICAL MECHANISMS OF RADIATION-INDUCED MITOCHONDRIAL DYSFUNCTION IN IRRADIATED ANIMALS DESCENDENTS

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Summary/Резюме

The purpose of the work is to investigate dose-dependent and organ-specific alterations in the activity of α-KGDH and SDH and the content of adenine nucleotides (ATP, ADP, AMP) in the liver, heart, and skeletal muscle of rat offspring born to parents irradiated with 3.0 and 5.82 Gy, and to determine their pathophysiological significance in mitochondrial dysfunction. The study was performed on the offspring of adult rats exposed to total г-irradiation at doses of 3.0 and 5.82 Gy. Mitochondrial fractions of the liver, myocardium, and skeletal muscle were analyzed for the activity of α-KGDH and SDH, as well as for adenylate nucleotide levels (ATP, ADP, AMP). Offspring of irradiated parents demonstrated a dose-dependent suppression of б-KGDH and SDH, with the most pronounced impairment observed in skeletal muscle. At 3.0 Gy, changes were moderate and partly compensatory, while at 5.82 Gy, systemic and profound inhibition of both dehydrogenases was detected, indicating mitochondrial bioenergetic collapse. In parallel, adenylate imbalance was observed, with ATP depletion accompanied by ADP and AMP accumulation, reflecting a decline in adenylate energy charge. Skeletal muscle exhibited the greatest vulnerability, showing combined dehydrogenase deficiency and a sharp decrease in ATP content. Parental γ--irradiation at doses of 3.0 and 5.82 Gy induces an energy-deficient phenotype in their offspring, characterized by dose-dependent inhibition of α-KGDH and SDH and disturbances of the adenylate pool. These findings highlight the central role of TCA cycle dehydrogenases in radiation-induced mitochondrial dysfunction and support their potential as early biomarkers of radiation-related metabolic impairment.

Key words: *г-irradiation, irradiated animals descendents, mitochondrial dysfunction,*