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MORPHOLOGICAL CHANGES OF THE ADRENAL GLAND IN RATS UNDER CONDITIONS OF EXPERIMENTAL CHRONIC HYPERGLYCEMIA

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Diabetes-related diseases are the cause of disability and death of millions of people in the world. Hyperglycemia leads to disturbances in carbohydrate, fat, and protein metabolism and significant energy deficit. The morphological features of the structure of the adrenal gland under the conditions of alloxan-induced hyperglycemia require a more detailed study and will allow to understand the mechanisms of neurohumoral regulation in diabetes. The aim of the study was to determine the morphological changes of the adrenal gland in young rats under conditions of alloxan-induced chronic hyperglycemia. The research was conducted on 40 white laboratory rats aged 3-4 months, which were divided into 3 groups: control, experimental (with a period of chronic hyperglycemia of 30 days), experimental (with a period of chronic hyperglycemia of 60 days). Type 1 diabetes was modeled using the chemical alloxan. Preparation of histological slides was carried out according to generally accepted methods. Under the conditions of chronic hyperglycemia on the 30th day of the experiment, histological studies of the adrenal gland showed that some endocrinocytes were destructively changed, there were signs of swelling in the cytoplasm of cells, the appearance of "light" and "dark" endocrinocytes, and the vessels were filled with blood and dilated. On the 60th day of the experiment, changes in the organ become more pronounced – the connective tissue capsule was thickened and stratified, endocrinocytes are destructively and dystrophically altered, cytoplasmic swelling and nuclear pyknosis, the number of lipid droplets was insignificant. It was established that the vessels were filled of blood, with the phenomenon of the sludge effect of erythrocytes and diapedesis of leukocytes, perivascular edema accompanied by dystrophy of endocrinocytes, which indicates significant disorders of the functional activity of the organ and exhaustion of its adaptive reserves.

Key words: *hyperglycemia, alloxan, adrenal gland, endocrinocytes, histological changes.*

Connection of the publication with planned research works. The work is the fragment of the planned research work «Morphofunctional aspects of the violation of the homeostasis of the organism», state registration number 0118U006611.

Introduction. Today, diabetes is one of the most common diseases of mankind, it ranks third in the world after diseases of the cardiovascular system and oncological pathologies [1, 2, 3]. The number of patients is increasing every year, and diabetes-related diseases are the cause of disability and death of millions of people in the world [4, 5]. Hyperglycemia occurs as a result of an acute insulin deficiency, which leads to disturbances in carbohydrate, fat, and protein metabolism and a significant energy deficit [6]. One of the most important risk factors for damage to the organs of the endocrine system in diabetes is precisely chronic hyperglycemia, which leads to structural and functional changes in the organs of all body systems and, in particular, the adrenal gland, which is stress-sensitive organ [7, 8, 9, 10, 11]. The pathomorphology of various organs under conditions of experimental hyperglycemia has been described by many researchers, but the morphological features of the structure of this organ under conditions of alloxan-induced hyperglycemia require a more detailed study and will allow to understand the mechanisms of neurohumoral regulation in diabetes. In recent years, researchers have modeled this disease using various methods [12, 13, 14]. Chemical and surgical methods are considered the most common. Alloxan, as a product of the breakdown of uric acid, is a physiologically active substance that causes necrosis of B-cells of the endocrine part of the pancreas. In addition to the pathological effect on the pancreas, alloxan causes disturbances in metabolism and microcirculation in organs. Despite numerous studies of the effect of hyperglycemia on organ remodeling, the morphological state of the adrenal glands under the conditions of alloxan-induced chronic hyperglycemia is insufficiently studied and requires more detailed research.

Therefore, **the aim of our study** was to establish the morphological features of the structure of the adrenal glands in young rats under conditions of alloxan-induced chronic hyperglycemia.

Object and methods of research. The study was performed on 40 white laboratory rats aged 3-4 months, which were divided into groups: I – control, II – experimental (with a period of chronic hyperglycemia of 30 days), III – experimental (with a period of chronic hyperglycemia of 60 days). The experiment was simulated using a chemical model of type 1 diabetes (using the chemical substance alloxan) [14]. Rats of the experimental group, after a 10-hour fasting, against the background of normal blood glucose level (3.5-6.3 mmol/l), were put into a state of chronic hyperglycemia with the help of a intraperitoneal injection of a alloxan dihydrate solution once in a dose of 20 mg/100 g of mass body in a 0.9% solution of sodium chloride. Animals were taken out of the experiment on days 30 and 60 by decapitation. The experiment on animals was carried out in compliance with the international rules and principles of the «European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes» (Strasbourg, France, 1986) and the Law of Ukraine dated

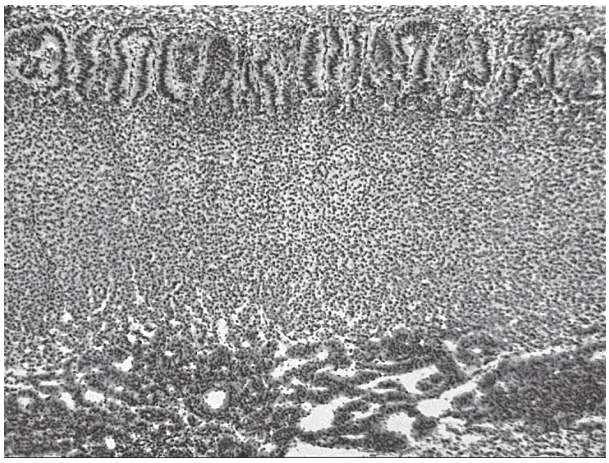

Figure 1 – Microscopic structure of the adrenal gland in rats of the control group. Connective tissue capsule, zona glomerulosa, zona fasciculata, zona reticularis, medulla. Staining with hematoxylin-eosin. Magnification: x100.

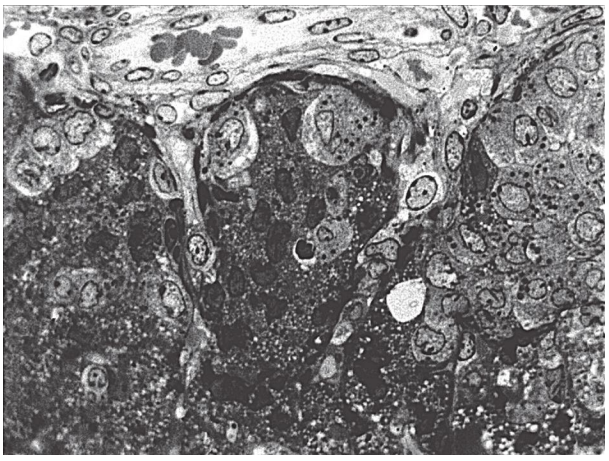

Figure 2 – Microscopic changes in the zona glomerulosa of the adrenal gland cortex in animals with a period of chronic hyperglycemia of 30 days. Blood-filled venule in capsule, destructively changed "light" and "dark" endocrinocytes. Staining with methylene blue. Magnification: x400.

February 21st, 2006 No. 3447-IV «On the Protection of Animals from Cruelty». For histological examination, the cortex and medulla of the adrenal gland were collected, fixed in 10% neutral buffered formalin tissue dehydration was carried out in alcohols of increasing concentration, soaked in isopropyl alcohol and three series of paraffin. The material was embedded into paraffin blocks. Sections with a thickness of 6-10 μm were obtained using a Reichert microtome. Histological sections were dried on glass slides, deparaffinized and dehydrated. Staining was carried out with hematoxylin-eosin, enclosed in polystyrene [15]. To make semi-thin sections with a thickness of 1-2 microns, the tissue was fixed in a 2.5% glutaraldehyde solution with a medium pH of 7.3-7.4. Postfixation was carried out in a 1% solution of osmium tetroxide, dehydration was done in alcohols of increasing concentration and poured into a mixture of epoxy resins. Semi-thin sections were made on an LKB 4801 A ultramicrotome and stained with methylene blue. Histological analysis and photography of the sections were performed using the light microscope Olympus BX63 (Japan) at magnifications of 100, 200, 400 times and videocamera Baumer/optronic Type: CX 05c (Switzerland) [16, 17].

Research results and their discussion. When examining the adrenal gland of animals in the control group, a connective tissue capsule was determined, in which blood vessels and clearly separated cortex and medulla of the organ were identified. The zona glomerulosa was formed by endocrinocytes of oval, elongated and polygonal shape, which formed groups in the shape of arches and curved cords, between which there were connective tissue layers with numerous blood capillaries in them. The majority of endocrinocytes had a relatively light, eccentrically located rounded nuclei with clumps of chromatin in the karyoplasm, the cytoplasm of the cells was oxyphilic. On the slides stained with methylene blue, lipid droplets of different sizes with a homogeneous matrix were determined in the cytoplasm of cells. The zona fasciculata was formed by cells that were grouped into elongated parallel fascicles. Most of the endocrinocytes in it had light oval nuclei with a clear nucleoli located eccentrically, light eosinophilic cytoplasm and a small number of vacuoles. A large number of lipid inclusions was present in the cytoplasm of the cells. The zona reticularis of the adrenal cortex was represented by compactly packed endocrinocytes of various shapes with dark hyperchromic nuclei, clear nucleoli and diffusely located clumps of chromatin. Lipid droplets had a similar appearance and size as in other zones of the cortex, but

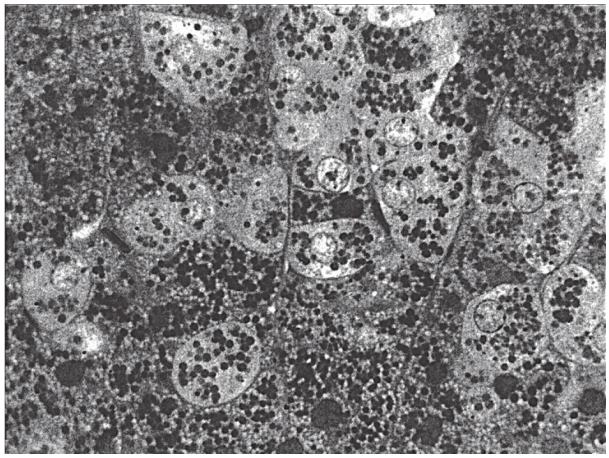

Figure 3 – Microscopic changes in the zona fasciculata of the adrenal gland cortex in animals with a period of chronic hyperglycemia of 30 days. "Light" endocrinocytes, "dark" cells with pyknotic nuclei, endocrinocytes with a moderate number of lipid droplets. Staining with methylene blue. Magnification: x400.

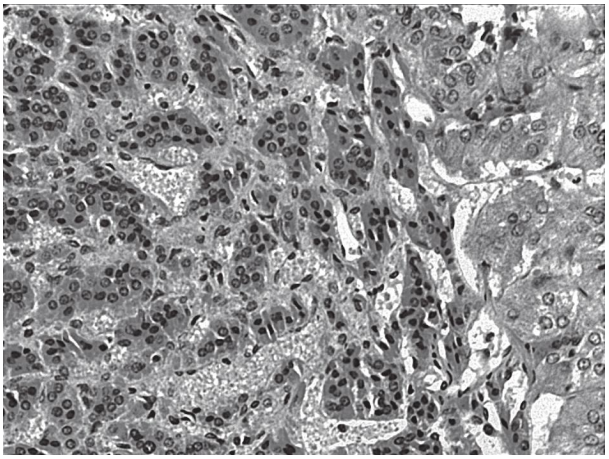

Figure 4 – Histological changes of the zona reticularis of the adrenal gland cortex in animals with a period of chronic hyperglycemia of 30 days. Dilated blood-filled vessels, endocrinocytes with pyknotic nuclei, interstitial edema. Staining with hematoxylin-eosin. Magnification: x400.

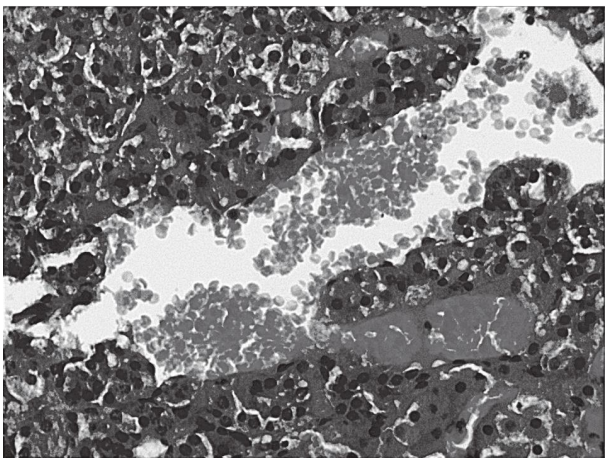

Figure 5 – Microscopic changes of the adrenal gland medulla in animals with chronic hyperglycemia for 30 days. Blood-filled sinusoidal hemocapillaries, destruction of chromaffinocytes. Staining with hematoxylin-eosin. Magnification: x400.

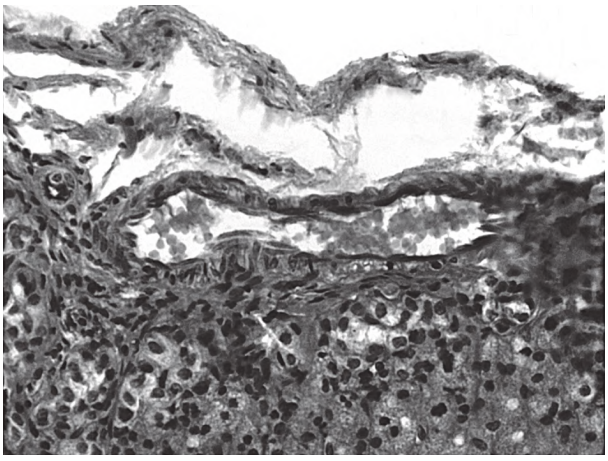

Figure 6 – Histological changes of the zona glomerulosa of the adrenal gland cortex in animals with a period of chronic hyperglycemia of 60 days. Deformed capsule, vessel in capsule, destructively changed endocrinocytes. Staining with hematoxylin-eosin. Magnification: x400.

they were less numerous. The cortex and medulla were separated by a thin layer of loose connective tissue. The medulla of the organ was characterized by large cells – chromaffinocytes of rounded and polygonal shape with large light nuclei in the basophilic cytoplasm **(fig. 1)**. Between epinephrocytes and norepinephricocytes, numerous blood vessels with a wide lumen were visible – sinusoidal capillaries and venules that were moderately filled with blood.

When examining the adrenal gland in animals of the second group (with a period of chronic hyperglycemia of 30 days), the following morphological changes were established. The connective tissue capsule of the organ is partially thickened and stratified. The vessels of the capsule were dilated and filled with blood. The wall of the arteriole in capsule was destructively changed, the internal elastic membrane was unclear, discontinuous. The media of vessel was thickened, with signs of edema, the connective tissue elements of the adventitia were disorganized. Perivascular edema was present. Zones of the cortex were clearly defined, but changes in the architecture of the organ were observed in some places. Blood-filled capillaries were found in all zones of the cortex, but they were most abundant in the zona reticularis. There were distinct destructive changes in the cortex of the adrenal gland, but the most pronounced in the zona fasciculata of it. In the zona glomerulosa, some endocrinocytes had indistinct contours of cell membranes, oxyphilic fine-grained cytoplasm, and round-oval nuclei that were hyperchromic. The nuclei of some cells had an irregular star shape with uneven contours of the karyolemma. Slight cell swelling was detected. «Light» and «dark» endocrinocytes were observed. Single destructively changed cells with the phenomenon of vacuolar dystrophy were present, they contained light nuclei, the cytoplasm was filled with numerous vacuoles **(fig. 2)**.

The zona fasciculata contained cells of various shapes and sizes, the cell membranes of which were not clearly visualized. Predominantly «light» endocrinocytes in the zona fasciculata were observed, which had oxyphilic cytoplasm, rounded light nuclei and significantly vacuolated cytoplasm, there were also «dark» cells with pyknotic hyperchromic nuclei located eccentrically and clearly contoured karyolemma. The cytoplasm of the cells contained a significant amount of lipid inclusions. However, there were cells with a small number of lipid droplets that unevenly filled the cytoplasm around the nucleus. The cytoplasm of some endocrinocytes was unevenly stained,

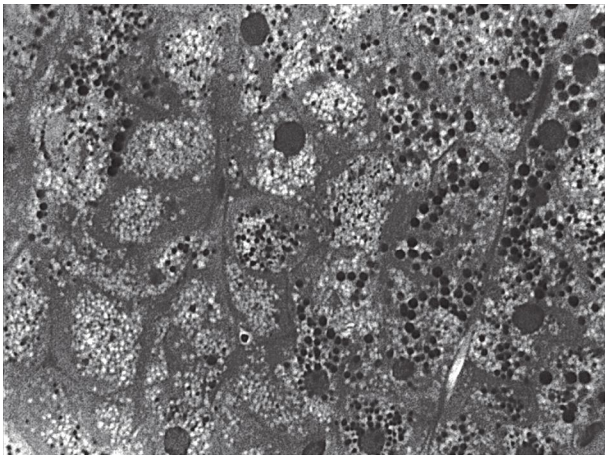

Figure 7 – Microscopic changes in the zona fasciculata of the adrenal gland cortex of animals with a period of chronic hyperglycemia of 60 days. "Light" endocrinocytes, "dark" endocrinocytes, cells without lipid inclusions. Staining with methylene blue. Magnification: x400.

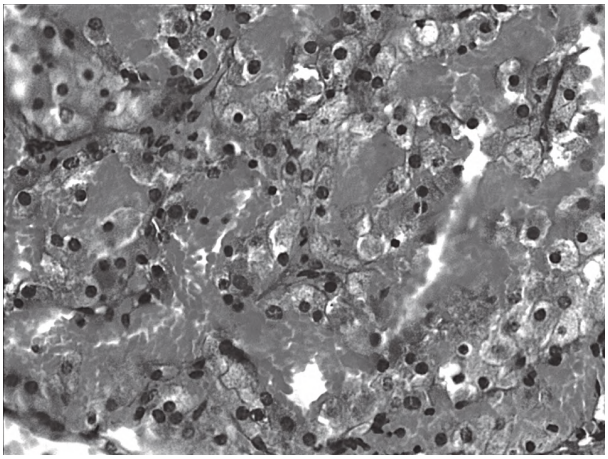

Figure 8 – Histological changes of the zona reticularis of the adrenal gland cortex in animals with a period of chronic hyperglycemia of 60 days. Dilated blood-filled vessels, destructively changed endocrinocytes with pyknotic nuclei. Staining with hematoxylin-eosin. Magnification: x400.

the nuclei were pyknotically altered, with clear clumps of heterochromatin in the karyoplasm **(fig. 3)**.

The vessels of the microcirculatory bed of the zona reticularis were significantly dilated and filled with blood, with moderate perivascular edema, which indicates a violation of microcirculation. The endocrinocytes of the zone lost their order in some places. The polygonal cells of the zone contained significantly vacuolated cytoplasm and hypertrophied dark nuclei **(fig. 4)**. Single hemorrhages were present. The connective tissue layer between the cortex and medulla was thickened in some areas.

The chromaffinocytes of the medulla of the organ contained large cells with intensively eosinophilic, moderately vacuolated cytoplasm and large, light, oval-shaped nuclei containing one or two nucleoli and clear contours of nuclear membranes. However, there were some cells with signs of cytoplasmic edema and vacuolar dystrophy, pyknotically altered nuclei. In some endocrinocytes, the integrity of the cell membranes was broken. The venules of the medulla were expanded, with the erythrocyte sludge phenomenon, diapedesis of leukocytes, and perivascular edema **(fig. 5)**. Basement membrane and endothelial lining was with moderate destructive changes.

Histological studies of adrenal gland in animals of the third experimental group (with a term of chronic hyperglycemia of 60 days) showed more significant destructive changes compared to the previous term of the study. The connective tissue capsule of the organ was thickened, in some places stratified, swollen. Arterioles and hemocapillaries of the capsule were expanded, full of blood. Dyscomplexation of endocrinocytes in the organ and architectural disturbances were observed. In the zona glomerulosa, endocrinocytes were randomly located. The glomeruli had different shapes and sizes. There were areas of necrotic cell changes and overgrowth of the connective tissue component. The contours of the cell membranes due to cell swelling were indistinct. Cytoplasm of most cells was clear, eosinophilic, nuclei were hyperchromic, clearly contoured, some with signs of pyknosis. There were few lipid inclusions in the cytoplasm. Dystrophically altered endocrinocytes were also observed **(fig. 6)**.

The zona fasciculata was formed by «dark» endocrinocytes with cytoplasm that had signs of hypertrophy. Round-oval shaped nuclei were basophilic, hyperchromic, with clear contours of nuclear membranes and were located eccentrically. In most cells, numerous vacuoles of various sizes were found in the cytoplasm. The nuclei of such cells were hypertrophied, swollen, with clumps of condensed heterochromatin and an indistinct nucleolus. There were also «light» cells that had an intensively enlightened, oxyphilic cytoplasm, with signs of granular, vacuolar dystrophy. Rounded, moderately basophilic nuclei located eccentrically were determined. The number of lipid inclusions in the zona fasciculata is insignificant compared to the control. Some cells practically did not contain lipid droplets, but such cells were detected infrequently **(fig. 7)**.

Individual necrotically altered endocrinocytes were observed. The wall of the blood capillaries of the zona fasciculata was with perivascular edema.

The vessels of the microcirculatory bed of the zona reticularis were filled with blood and dilated with signs of sludge phenomenon and adhesion of formic elements

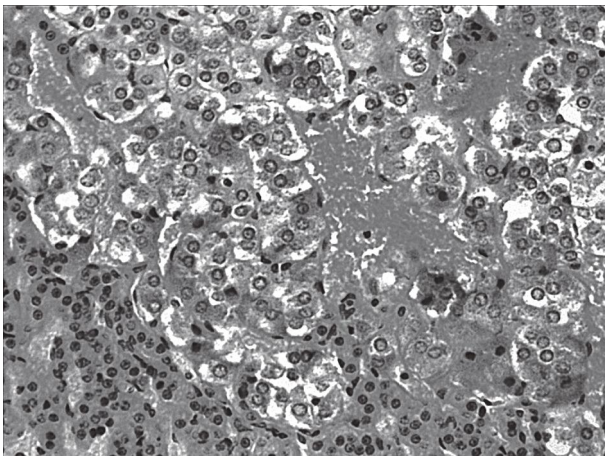

Figure 9 – Microscopic changes of the adrenal gland medulla in animals with chronic hyperglycemia for 60 days. Blood-filled sinusoidal hemocapillaries, destructively changed chromaffinocytes. Staining with hematoxylin-eosin. Magnification: x400.

to the capillary wall. Both «light» and «dark» spongiocytes were observed. Small polygonal cells with dark basophilic nuclei and indistinct nucleoli were found. There were practically no lipid inclusions in the cytoplasm of cells. The sinusoidal capillaries of the zone were both narrowed and unevenly expanded, filled with blood, with the phenomenon of stasis and perivascular edema **(fig. 8)**.

The medulla of the organ contained a large number of large, oval-shaped chromaffinocytes with well-defined light nuclei and vacuolated, enlightened cytoplasm. However, there were destructively altered endocrinocytes with cytoplasmic swelling and signs of vacuolar dystrophy. Nuclei are hyperchromic, pyknotic, irregularly shaped. In this area, a large number of vessels – venules and capillaries with an expanded lumen and a large number of shaped elements were observed **(fig. 9)**. The media of such vessels showed signs of swelling of myocytes, the collagen fibers of the adventitia were stratified.

Conclusions. Thus, it was established that under the conditions of chronic hyperglycemia already on the 30th day of the experiment, histological studies of the adrenal gland showed the following morphological changes – endocrinocytes were destructively changed, there were signs of swelling of the cytoplasm in cells, the appearance of «light» and «dark» endocrinocytes also was established. The presence of blood-filled and dilated vessels indicates a violation of microcirculation in the organ. As the duration of hyperglycemia increases, the detected changes in the organ become more pronounced – the connective tissue capsule was thickened and stratified, endocrinocytes were destructively and dystrophically altered with cytoplasmic swelling and pyknotically altered nuclei. A small amount of lipid droplets was found in endocrinocytes. Vascular disorders manifested by plethora, with the phenomenon of the sludge effect of erythrocytes and diapedesis of leukocytes, perivascular edema, as well as remodeling of endocrinocytes indicated significant disorders of the functional activity of the organ and exhaustion of its adaptive reserves.

Prospects for further research. Peculiarities of the submicroscopic structure of the adrenal gland under the conditions of alloxan-induced diabetes require further research.

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МОРФОЛОГІЧНІ ЗМІНИ НАДНИРКОВИХ ЗАЛОЗ ЩУРІВ ЗА УМОВ ЕКСПЕРИМЕНТАЛЬНОЇ ХРОНІЧНОЇ ГІПЕРГЛІКЕМІЇ

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Резюме. На сьогодні цукровий діабет є однією з найпоширеніших хвороб людства, він займає третє місце в світі після захворювань серцево-судинної системи та онкологічних патологій. Хронічна гіперглікемія, що призводить до структурно-функціональних змін в органах усіх систем організму і, зокрема, надниркових залозах, які є стрес чутливими органами. Тому метою нашого дослідження було встановити морфологічні зміни надниркових залоз у щурів молодого віку за умов алоксан-індукованої хронічної гіперглікемії.

Дослідження проводили на 40 білих лабораторних щурах віком 3-4 місяці, які були поділені на групи: I – контрольна, II – експериментальна (з терміном хронічної гіперглікемії 30 діб), III – експериментальна (з терміном хронічної гіперглікемії 60 діб). Експеримент моделювали з використанням хімічної моделі цукрового діабету 1 типу (із застосуванням хімічної речовини алоксан). Тварин виводили з експерименту на 30 та 60 добу шляхом декапітації та вивчали мікроскопічні зміни в кірковій та мозковій речовині надниркових залоз. Гістологічний аналіз та фотографування зрізів проводили із використанням мікроскопа Olympus BX63 (Japan) за збільшення 100, 200 та 400. Встановлено, що на 30 добу експерименту сполучнотканинна капсула органу була частково потовщена та розшарована, подекуди спостерігались зміни архітектоніки органу, ендокриноцити були деструктивно змінені, ядра деяких клітин пікнотичні гіперхромні, наявні ознаки набряку цитоплазми клітин, встановлено появу "світлих" і "темних" ендокриноцитів в кірковій речовині залози. Деякі хромафіноцити мозкової речовини органу мали ознаки набряку та вакуольної дистрофії цитоплазми. Наявність кровонаповнених та розширених судин свідчить про порушення мікроциркуляції в органі. На 60-ту добу дослідження виявлені більш значні деструктивні зміни – сполучнотканинна капсула була потовщена, розшарована та набрякла, ендокриноцити деструктивно та дистрофічно змінені із набряком цитоплазми та пікнотично зміненими ядрами. Встановлена незначна кількість ліпідних крапель в ендокриноцитах. Виявлені судинні розлади, що проявлялись повнокров'ям, із явищем сладж ефекту еритроцитів та діапедезу лейкоцитів, периваскулярним набряком, супроводжувались ремоделюванням ендокриноцитів як кіркової так і мозкової речовини, що свідчить про значні розлади функціональної активності органа та виснаження його адаптаційних резервів.

Ключові слова: гіперглікемія, алоксан, надниркові залози, ендокриноцити, гістологічні зміни.

MORPHOLOGICAL CHANGES OF THE ADRENAL GLAND IN RATS UNDER CONDITIONS OF EXPERIMENTAL CHRONIC HYPERGLYCEMIA

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Abstract. Today, diabetes is one of the most common diseases of mankind, it ranks third in the world after diseases of the cardiovascular system and oncological pathologies. Chronic hyperglycemia, which leads to structural and functional changes in the organs of all body systems and, in particular, the adrenal gland, which is stress-sensitive

organs. Therefore, the aim of our study was to determine the morphological changes of adrenal glands in young rats under conditions of alloxan-induced chronic hyperglycemia.

The study was conducted on 40 white laboratory rats aged 3-4 months, which were divided into groups: I – control, II – experimental (with a period of chronic hyperglycemia of 30 days), III – experimental (with a period of chronic hyperglycemia of 60 days). The experiment was simulated using a chemical model of type 1 diabetes (using the chemical substance alloxan). Animals were removed from the experiment on the 30th and 60th day by decapitation, and microscopic changes in the cortex and medulla of the adrenal gland were studied. Histological analysis and photography of the sections were carried out using an Olympus BX63 (Japan) microscope at magnifications of 100, 200 and 400. It was established that on the 30th day of the experiment, the connective tissue capsule of the organ was partially thickened and stratified, changes in the architecture of the organ were observed in some places, endocrinocytes were destructively changed, nuclei some cells are pyknotic hyperchromic, there are signs of swelling of the cytoplasm of cells, the appearance of «light» and «dark» endocrinocytes in the cortex of the gland is established. Some chromaffinocytes of the medulla of the organ had signs of edema and vacuolar dystrophy of the cytoplasm. The presence of blood-filled and dilated vessels indicates a violation of microcirculation in the organ. On the 60th day of the study, more significant destructive changes were detected – the connective tissue capsule was thickened, stratified and swollen, endocrinocytes were destructively and dystrophically changed with swelling of the cytoplasm and pyknotically changed nuclei. A small amount of lipid droplets was found in endocrinocytes. Vascular disorders manifested by plethora, with the phenomenon of sludge effect of erythrocytes and diapedesis of leukocytes, perivascular edema, were accompanied by remodeling of endocrinocytes of both adrenal cortex and medulla, which indicates significant disorders of the functional activity of the organ and exhaustion of its adaptive reserves.

Key words: hyperglycemia, alloxan, adrenal gland, endocrinocytes, histological changes.

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The authors declare no conflict of interest.

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MORPHOMETRIC ASPECTS OF STUDY OF FEATURES OF REMODELING OF MICROVESSELS OF SYNOVIAL MEMBRANE OF THE KNEE JOINT AT DIABETIC ARTHROPATHY

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Diabetes mellitus often leads to joint damage, the morphogenesis of which is insufficiently studied. The aim of the study was the morphometric study of the features of remodeling of microvessels of the synovial membrane in experimental diabetic arthropathy of the knee joint. Microvessels of the synovial membrane of the knee joint of 60 sexually mature white male rats, divided into 3 groups, were studied by morphological and morphometric methods. The 1st group included 20 intact animals, the 2nd – 20 rats with one-month diabetic arthropathy of the knee joint, the 3rd – 20 experimental animals with the two-month specified pathology. A single intraperitoneal injection of streptozotocin simulated hyperglycemia from the company "Sigma" at 50 mg/kg. Rats were euthanized by bloodletting under Sodium thiopental anesthesia one month and two months after the start of the experiment. The vessels of