дорослих білих щурах-самцях лінії Вістар з масою тіла 260-300 грамів, віком 10-12 місяців. Дослідження показало, що строма великих слинних залоз щурів представлена аморфною речовиною, колагеновими волокнами і відростками фібробластів між сусідніми кінцевими відділами часточок; тіла фібробластів розміщені у вузлових інтерстиційних відсіках – місцях контакту 3-4 кінцевих відділів. Із судин гемомікроцир-куляторного русла навколо кінцевих відділів часточок переважають капіляри і пост капіляри, у перипротоковій сполучній тканині – посткапіляри і венули. У стромі великих слинних залоз щурів місцевий захисний бар'єр переважно представлений плазмоцитами і макрофагами в міжацинарному інтерстиції та макрофагами і мастоцитами в перипротоковій сполучній тканині.

Ключові слова: слинні залози, строма, щури.

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взрослых белых крысах-самцах линии Вистар с массой тела 260-300 граммов и возрастом 10-12 месяцев. Исследование показало, что строма больших слюнных желез крыс представлена аморфным веществом, коллагеновыми волокнами и отростками фибробластов; тела фибробластов расположені в узловых интерстициальных отсеках – местах контакта 3-4 конечных отделов. Из сосудов гемомикроциркуляторного русла вокруг конечных отделов долек преобладают капилляры и посткапилляры, в перипротоковой соединительной ткани – посткапилляры и венулы. В строме больших слюнных желез крыс местный защитный барьер преимущественно представлен плазмоцитами и макрофагами в межацинарном интерстиции и макрофагами и мастоцитами в перипротоковой соединительной ткани.

Ключевые слова: слюнные железы, строма, крысы.

Рецензент

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NALBUPHINE-INDUCED SUBMICROSCOPIC CHANGES IN THE COMPONENTS OF THE THYMUS VASCULAR BED

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Notwithstanding the widespread use of opioid analgesics in medical practice and the increased incidence of drug addiction, especially among teenagers, the issue of the influence of opioids on the immune organs remains relevant.

52 white male rats of reproductive age with an initial body weight of 140–150 g were involved into study. Nalbuphine was administered intramuscularly once daily at 10:00 –11:00 hours during 42 days, increasing the dose every 7 days. The material was collected in accordance with conventional technique.

After one week of the introduction of Nalbuphine a moderate thickening of the basal membrane and enlargement of the lumen of blood capillaries was observed. Within the two weeks the lumen of arteries, arterioles and venules was slightly dilated, the nuclei of the endotheliocytes were slightly enlarged, occupying a significant portion of the cytoplasm; invaginations were formed by the karyolemma. After three to four weeks the veins and venules were dilated, plethoric, interendothelial bonds in the vascular wall were enlarged, the basal membrane was damaged, deformed red blood cells were found in the lumen of the hemocapillaries, arranged in the "coin column", often attached to the luminal surface of the endotheliocytes. The wall of arteries and arterioles were thickened due to the edema of endotheliocytes and initial signs of sclerosis. After five to six weeks the perivascular edemas and hemorrhages into the parenchyma thymus was detected. The vast majority of vessels vere "empty". One week after the drug was discontinued, no irreversible changes were found.

Key words: nalbuphine, rat, vein, artery, blood capillary, endothelial cell, pericyte

The research is a part of complex topics, entitled "Features of the structural organization of the lymphoid organs and vascular bed in ontogenesis in the norm and the regularities of their reorganization under the action of antigens, chemical and physical factors on the organism" – the State registration number 0115U003903 and "Structure of organs and their bloodstream in ontogenesis, under the influence of laser irradiation and pharmaceuticals, with violations of blood supply, reconstructive operations and diabetes" – the State registration number 0110U001854.

For a long time opioid analgesics have been used for therapeutic purposes in medical practice [6, 9, 10]. Recently, experimental studies have been conducted on the impact of these drugs on certain organs and tissues (eyeball, tongue, cerebellum, ulcer, pancreas, skin) [1, 3, 5, 7, 8]. However, in the scientific literature, no data on the effect of narcotic analgesics on the organs of the immune system have been found to date. The primary immune organs include the thymus, where antigen-independent proliferation and differentiation of subpopulations of T-lymphocytes occurs. From thymus T-lymphocytes enter into the vascular bed, spreading to T-dependent zones of the secondary immune organs [4]. The latter provide an adequate response of the body to the penetration of foreign antigens. Therefore, the study of the effect of opioids on the structure of the thymus is the relevant medical issue.

The paper is aimed at the study of the features of submicroscopic changes of the components of the thymus vascular bed of white male rats of reproductive age in the dynamics of six-week exposure to opioid nalbuphine and within one week after its discontinuation.

Material and methods. 52 white male rats of reproductive age with initial weight of 140-150 g were involved into study. Nalbuphine was administered intramuscularly once daily at the same period of

time (10:00-11:00) during 42 days, increasing the dose every 7 days. Experimental animals were divided into 8 groups: Group I (n=5) involved intact animals; Group II (n=5) animals were administered intramuscularly with 8 mg/kg nalbuphine opioid daily for one week; Group III (n=5) animals were administered with 15 mg/kg nalbuphine during the second week; Group IV (n=5) animals were administered with 20 mg/kg nalbuphine during the third week; Group V (n=5) animals were administered with 25 mg/kg nalbuphine during the fourth week; Group VI (n=5) animals were administered with 30 mg/kg nalbuphine during the fifth week; Group VII (n=5) animals were administered with 35 mg/kg nalbuphine during the sixth week; the material from Group VIII (n=5) animals were taken within one week after the drug was discontinued. The controls were 12 white male rats, administered with 0,9 % sodium chloride solution. Nalbuphine was administered in compliance with the patent №76564 U Ukraine "Method for the simulation of physical opioid dependence in rats" [2].

The material was collected according to the conventional technique. The sections were made on UMTP–6M ultramicrotome, using the diamond knife, (DIATOM) and double-contrasted with Reynolds and uranyl acetate. The thymus sections were investigated using the electronic transmissive microscope TEM–100. The photocoded material was examined using the SONY–H9 digital camera.

Results and discussion. Blood is supplied to the thymus of white rats with from numerous branches of the thymus gland, bifurcating into the interlobular and intralobular arteries. The arcuate arteries are branched from these vessels, forming the vessels of the hemomicrocirculatory bed.

The electron microscopic study of the thymus of white male rats of reproductive age showed that one week after administration of nalbuphine a moderate thickening of the basal membrane and enlargement of the lumen of the blood capillaries was observed. On the luminal surface of the endothelial cells cytoplasmic projections were found. The nuclei of the endothelial cells were elongated; euchromatin predominated in the karyoplasma (Fig. 1). Submicroscopically, the nucleolus was well contoured. The nuclear shell (karyolemma) was even, without protrusions. In the cytoplasm, organelles were clearly differentiated. Mitochondria, Golgi complex, endoplasmic reticulum, ribosomes were unchanged. Submicroscopically, the veins and venules were slightly enlarged. The diameter of the arteries was unchanged. During the observation period, the structural organization of the walls of arterioles and venules was unchanged; however, perivascular edema was noted.

After two weeks of exposure to nalbuphine the electronic microscopy of the thymus of white male rats of reproductive age has revealed the following ultrastructural changes: the lumen of the arteries, arterioles and venules was slightly enlarged, the nuclei of the endothelial cells were slightly enlarged, occupying a significant partion of the cytoplasm, and invaginations were formed by the karyolemma. The luminal surface of the endothelial cells formed numerous microvilli. Organelles in the cytoplasm of endothelial cells lost their contours. Lumen of veins was enlarged and filled with blood corpuscles. The diameter of vessels of microcirculatory bed was enlarged. Red blood cells in the lumen of blood capillaries were often arranged in "coin columns". Sporadic erythrocytes have been detected in the intercellular space, indicating about the damage to the walls of the vessels (Fig. 2). Enlargement of the capillaries was somewhat narrowed due to the edema of the endothelial cells and the protrusion of the plasmolemma into the lumen. Lumen of arterioles was slightly enlarged. Basal membrane venules were thickened in places.

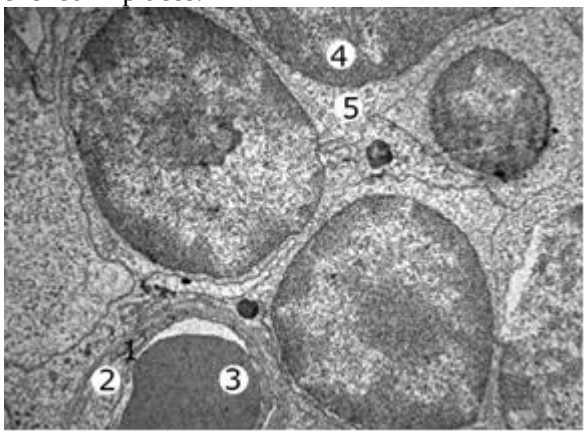

Figure 1. Cytoplasmic projections (1) on the lumen surface of the endothelial cell in the wall of the blood capillary in the cortical substance of the thymic lobules of white male rat within one week of administration of nalbuphine. 2 - nucleus of the endothelial cell; 3 - erythrocyte in the lumen of the blood capillary;4 - nucleus of thymocyte; 5 - thymocyte cytoplasm. Electronic microphotography. Magnification: × 6000.

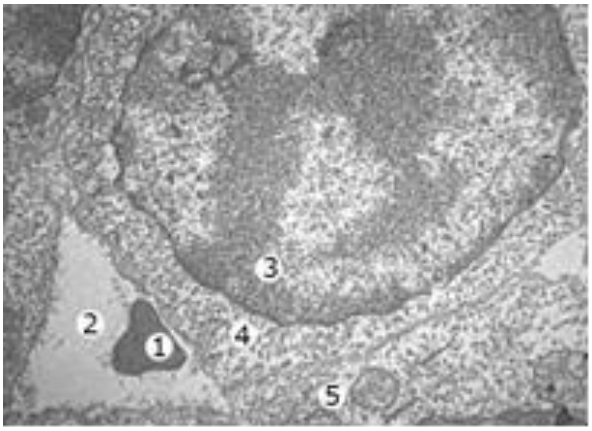

Figure 2. Ultrastructural changes in the medulla of the thymic lobules of white rat after two weeks of administration of nalbuphine. Erythrocyte (1) in the enlarged intercellular space (2), nucleus of thymocyte (3), cytoplasm of thymocyte (4), mitochondria (5). Magnification: × 8000.

After three weeks of administration of nalbuphine the electron microscopic study revealed changes in the components of the microcirculatory bed. The enlargement of the lumen of the venules and their blood filling was noted. Basal membrane of arterioles, blood capillaries and venules was thickened in places, stratified and edematous, and the number of microvilli was increased on the luminal surface of the endothelial cells. The nuclei of most endothelial cells were elongated; uneven contours of the karyolemma were detected. Chromatin in the karyoplasm was distributed unevenly; the sites of the heterochromatin near the nuclear shell were detected. The areas of clearness and damaged organelles were found in the cytoplasm. The edema of pericyte nuclei, surrounded by the basal membrane of the blood capillaries, was also noted. The bonding between pericytes and basal membrane of blood capillaries was preserved (Fig. 3).

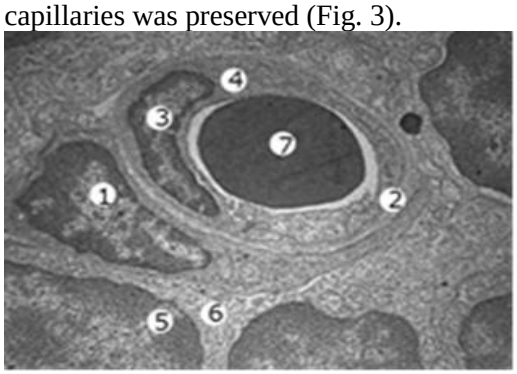

Figure 3. Submicroscopic changes in the cortical substance of the thymic lobules of white male rat after three weeks of administration of nalbuphine. Preserved bonding between the pericyte (1) and basal membrane (2) of blood capillaries. 3 – elongated nucleus of the endothelial cell, 4 – cytoplasm of endothelial cell; 5 – nucleus of thymocyte, 6 – cytoplasm of thymocyte, 7 – erythrocyte in the lumen of the blood capillary. Electronic microphotography. Magnification: × 6000.

Submicroscopically, it has been revealed that veins and venules were dilated, full-blooded, interendothelial bonds in the walls of the vessels were enlarged, the basal membrane was damaged, contributing to diapedesis of blood plasma through the wall of the vessel, causing the perivascular edema; the release of blood corpuscles into the parenchyma was noted. In the lumen of the blood capillaries the deformed erythrocytes, arranged in a "coin column", were often attached to the lumen surface of the endothelial cells. The wall of arteries and arterioles were thickened due to edema of the endothelial cells and initial signs of sclerosis. The most submicroscopic changes at this stage of the study were detected precisely in the blood capillaries. Their outer diameter was enlarged. Basal membrane of the blood capillaries was considerably thickened and stratified in places. In their lumen, the deformed erythrocytes were often arranged into clusters.

Electron-microscopically, after four weeks of the experiment, the nuclei of endothelial cells were enlarged in the wall of blood capillaries, which became irregularly elongated with protrusions and invaginations. Cytoplasm of the endothelial cells was thinned and cleared. The plasmolemma of the luminal surface of the endothelial cells formed numerous protrusions and microvilli in the lumen of the blood capillary, reducing their lumen. Mitochondria are cleared and enlarged. The Golgi complex is unstructured. Ultrastructurally, at this stage of the study, changes in all components of the thymus vascular bed were detected. Lumen of veins and venules were enlarged, vessels were deformed and full-blooded. Wall of arteries and arterioles were thickened, their lumen was narrowed. In the components of the hemomicrocirculatory bed the significant pathological changes have been found. Venules were full-blooded, interendothelial bonds were dilated; basal membrane was of uneven thickness. Perivascular edema was detected. The basal membrane of the blood capillaries was stratified and damaged in places. In the lumen of the blood vessels of the microcirculatory bed, red blood cells were altered, binding with the endothelial cells. Blood capillaries were also destructively altered. Edema and clearness of the endothelial cell cytoplasm was noted, which leads to a narrowing of the lumen of the capillaries; "empty" vessels were detected. In the lumen of some blood capillaries desquamated parts of the organelles and cytoplasm of the endothelial cells were noted. Additionally, submicroscopically, after five weeks of administration of nalbuphine, it was discovered that a large number of endothelial cells of the microvessels were unstructured, their nuclei were often damaged, with signs of pyknosis and karyorrhexis, and the nuclear membrane was disintegrated. In some endothelial cells the lysis of the cytoplasm was observed. The nucleus was darker due to the accumulation and predominance of heterochromatin. The lumen surface of the endothelial cells contained a large number of protrusions and microvilli with depressions in between. Mitochondria were enlarged and cleared, containing precipitates, and their membrane was loose. The destructive changes in the Golgi complex and the endoplasmic reticulum were revealed in the form of enlargements, absence of clear contours. The basal membrane was stratified, thickened, damaged in places. Interendothelial bonds were enlarged, partially damaged, forming the dipnoous defects of the wall. This leads to the release of the blood corpuscles into the parenchyma of the organ.

After six weeks of daily administration of nalbuphine the electron microscopic study of the thymus of white male rats revealed the further structural pathological changes in all components of the microcirculatory bed, which were irreversible. Veins and venules were enlarged, deformed, full-blooded. Lumen of vessels was filled with deformed erythrocytes with signs of aggregation and adhesion. Submicroscopically, in the wall of blood capillaries, venules and arterioles the edema of the endothelial

cells, local thickening of the basal membrane and its partial destruction was detected, which led to the formation of the dipnoous defects. It contributes to the perivascular edema and vascular hemorrhage (Fig. 4). The arteries and arterioles walls were thickened and their lumen was narrowed. The vast majority of vessels were "empty". In the components of the hemomicrocirculatory bed the deep destructive and degenerative changes were detected. Edema and clearness of the endothelial cell cytoplasm was noted, facilitating the narrowing of the lumen of the capillaries. The lumen was also narrowed due to the numerous protrusions of the luminal surface of the plasmolemma of the endothelial cells; at the cross-section the lumen was stellar-shaped. Some areas of the capillaries were so narrowed that they did not let the blood cells to pass. The endothelial plasmolemma was damaged; its nuclei had signs of karyorrhexis. The luminal surface of the endothelial cells contained numerous microvilli. Mitochondria were vacuolated, their matrix was cleared. The destructive changes in the elements of the Golgi complex were found; their membrane structures were destroyed. Similar destructive changes were detected in the granular endoplasmic reticulum, leading to the reduced number of tubules, making their size smaller.

Interendothelial bonds are dilated, partially damaged, forming the dipnoous defects of the wall. This leads to the release of the blood corpuscles in the parenchyma of the organ. The plasmolemma of the endothelial cells of the blood capillaries formed numerous dome-shaped protrusions and microvilli in their lumen. In many areas, the basal membrane of the blood capillaries was unclearly contoured, damaged and stratified in places. The bonding between the pericytes and basal membrane of blood capillaries was lost.

Within one week after the discontinuation of nalbuphine the electronic microscopy of the thymus particles of white male rats revealed structural changes similar to the previous experimental group of animals. The veins were dilated and deformed. Interendothelial bonds of the venules, blood capillaries and arterioles were dilated, the basal membrane was unevenly thickened; perivascular edema was noted. Reduced lumen, edema of the endothelial cell cytoplasm and local damage of the plasmolemma was specific for the blood capillaries. Venous hyperemia was detected. The dipnoous defects of the wall of the capillary were noted. In their lumen, red blood cells were altered with the signs of aggregation, adhesion and thrombosis. The wall of arteries and arterioles remained thickened with sclerotic alterations. Numerous "empty" vessels were found. In the components of the hemomicrocirculatory bed the deep destructive and degenerative changes were detected. Vessels with dipnoous defects of the wall were detected, which leads to the release of the blood corpuscles and plasma into the parenchyma of the gland, leading to edemas and hemorrhages (Fig. 5).

Cytoplasm of the endothelial cells in the blood capillaries is thinned, cleared, containing precipitates. The lumen of the blood capillaries was narrowed due to the numerous protrusions and microvilli of the cytolemma of the endothelial cells; at the cross-section the lumen was stellar-shaped. Some areas of the capillaries were so narrowed that they did not let the blood cells to pass. In some blood capillaries, the plasmolemma of endothelial cells formed huge protrusions into the lumen; others were damaged and without clear contours. In some cases the nuclei were enlarged, convex, and in others they were often damaged, with signs of karyorrhexis. The plasmolemma of the luminal surface of the endothelial cells contains a large number of protrusions, invaginations and microvilli. Mitochondria were vacuolated. The membrane was loose. The destructive changes of the Golgi complex, namely, the destruction of the membrane, and endoplasmic reticulum have been found, leading to the reduced number of tubules, making their size smaller.

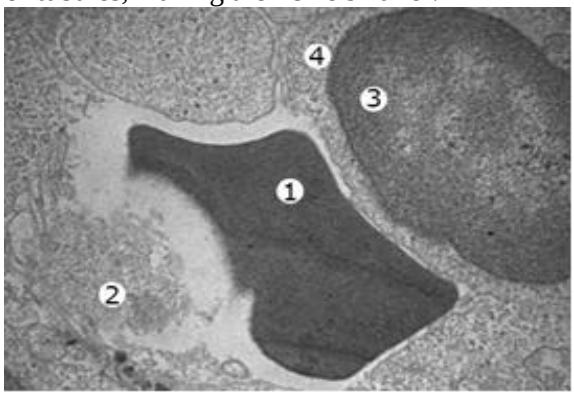

Figure 4. Deformed erythrocyte (1) in the parenchyma and destructive thymocytes (2) around the erythrocyte in the thymic lobules of white male rat after six weeks of administration of nalbuphine. 3 – nucleus of thymocyte; 4 – cytoplasm of thymocyte. Electronic microphotography. Magnification: × 6000.

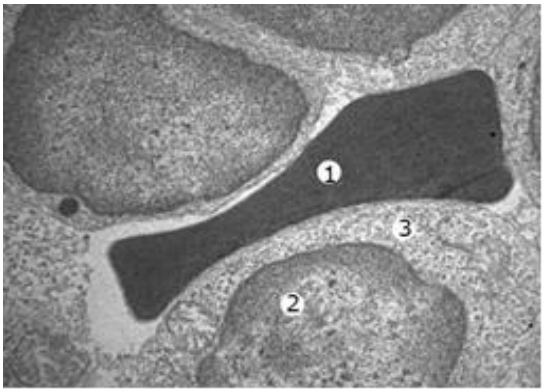

Figure 5. Deformed erythrocyte (1) in the parenchyma of thymus of white male rat within one week after discontinuation of nalbuphine. 2 – nucleus of thymocyte; 3 – cytoplasm of thymocyte. Electronic microphotography. Magnification: × 6000.

Conclusions

1. After one week of administration of nalbuphine moderate thickening of the basal membrane and enlargement of the lumen of the blood capillaries was observed;
2. After two weeks of the experiment, the lumen of the arteries, arterioles and venules was slightly dilated, the diameter of vessels in the microcirculatory bed was enlarged, red blood cells in the lumen of the blood capillaries were often arranged in a "coin column";
3. After three weeks of the experiment, the basal membrane of arterioles, blood capillaries and venules was thickened, stratified and swollen in places; the increased number of microvilli on the luminal surface of the endothelial cells was detected;
4. After four weeks of the experiment, changes in all components of the thymus vascular bed became more apparent;
5. After five and six weeks the edema of the endothelial cells, local thickening of the basal membrane and its partial destruction was detected in the wall of the blood capillaries, venules and arterioles, leading to the formation of dipnoous defects, which leads to perivascular edema and hemorrhages. Numerous vessels were "empty";
6. Within one week after discontinuation of nalbuphine, no irreversible changes were detected.

Perspectives of further research will encompass the establishment of the regularities of the nalbuphine-induced restructuring of the thymus vascular bed.

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Реферати

СУБМІКРОСКОПІЧНІ ЗМІНИ КОМПОНЕНТІВ СУДИННОГО РУСЛА ТИМУСА ПРИ ДІЇ НА ОРГАНІЗМ НАЛБУФІНУ

Гарапко Т. В., Головацький А. С.

Зважаючи на широке використання опіоїдних анальгетиків в медицині та зростання наркоманії, особливо серед підлітків, актуальним залишається питання впливу опіоїдів на імунні органи. Дослідження проведено на 52 білих щурах-самцях репродуктивного віку з початковою масою тіла 140–150 г. Препарат «Налбуфін» вводили внутрішньом′язово 1 раз на добу о 10–11 годині протягом 42 діб, підвищуючи дозу кожні 7 діб. Забір матеріалу проводили згідно загальноприйнятих правил. Через один тиждень введення налбуфіну спостерігалось помірне потовщення базальної мембрани та розширення просвіту кровоносних капілярів. Через два тижні просвіти артерій, артеріол та венул незначно розширені, ядра ендотеліоцитів дещо збільшені, займають значну частину цитоплазми, каріолема утворює інвагінації. Через три-чотири тижні вени і венули розширені, повнокровні, міжендотеліальні

СУБМИКРОКОПИЧЕСКИЕ ИЗМЕНЕНИЯ КОМПОНЕНТОВ СОСУДИСТОГО РУСЛА ТИМУСА ПРИ ВОЗДЕЙСТВИИ НА ОРГАНИЗМ НАЛБУФИНА

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Несмотря на широкое использование опиоидных анальгетиков в медицине и рост наркомании, особенно среди подростков, актуальным остается вопрос влияния опиоидов на иммунные органы. Исследование проведено на 52 белых крысах-самцах репродуктивного возраста с начальной массой тела 140–150 г. Препарат «Налбуфин» вводили внутр.-мышечно 1 раз в сутки в 10–11 часов в течение 42 суток, повышая дозу каждые 7 дней.. Забор материала проводили согласно общепринятым правилам. Через одну неделю введения налбуфина наблюдалось умеренное утолщение базальной мембраны и расширение просвета кровеносных капилляров. Через две недели просвет артерий, артериол и венул незначительно расширен, ядра эндотелиоцитов несколько увеличены, занимают значительную часть цитоплазмы, кариолема образует инвагинации. Через три-четыре недели вены и венулы расширены, полнокровные,

контакти в стінці судин розширені, базальна мембрана пошкоджена, у просвіті гемокапілярів деформовані еритроцити, розміщені «монетним стовпчиком», часто прикріплюються до люменальної поверхні ендотеліоцитів. Стінка артерій та артеріол потовщена в зв'язку з набряком ендотеліоцитів та початковими ознаками склерозу. Через п'ять-шість тижнів наколосудинні набряки та крововиливи в паренхіму тимуса. Переважна більшість судин «порожні». Через один тиждень після відміни препарату зворотних змін не виявлено.

Ключові слова: налбуфін, щур, вена, артерія, гемокапіляр, ендотеліоцит, перицит.

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междуэндотелиальные контакты в стенке сосудов расширены, базальная мембрана повреждена, в просвете гемокапилляров деформированные эритроциты, размещенные «монетным столбиком», часто прикрепляются к люменальной поверхности эндотелиоцитов. Стенка артерий и артериол утолщена в связи с отеком эндотелиоцитов и начальными признаками склероза. Через пять-шесть недель околососудистые отеки и кровоизлияния в паренхиму тимуса. Подавляющее большинство сосудов «пустые». Через одну неделю после отмены препарата обратных изменений не обнаружено.

Ключевые слова: налбуфин, крыса, вена, артерия, гемокапилляр, эндотелиоцит, перицит.

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CHANGES IN PERINEURIAL AND HEMATOENDONEURIAL BARRIERS OF THE SCIATIC NERVE IN PACLITAXEL-INDUCED PERIPHERAL NEUROPATHY

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The absence of a unified concept of paclitaxel-induced peripheral neuropathy morphogenesis determines the need for a detailed morphological study. This paper demonstrates ultramicroscopic changes in the structure of the perineurial and the hematoendoneurial barriers of the sciatic nerve in albino rats caused by paclitaxel. Chemotherapeutic agent was administered intraperitoneally at a dose of 2 mg/kg of body weight, each alternate day, 4 times. The experiment period was 120 days; during the experiment, samples were collected for morphometric study and electron microscopic study. In the experiment, there were determined changes in endoneurial blood flow manifested themselves as congestion, morphological signs of transendothelial transport abnormalities, dystrophic changes in endothelial cells of varying severity and stages, thickening and dissociation of the basement membrane. In the perineurium, the disorganization of fiber and cellular elements, deformation of the processes, hydropic dystrophy of perineurial cells and impaired permeability of the perineurium progressing within the first months of the experiment and gradually disappearing until the end of the experiment were observed.

Key words: Paclitaxel, perineurial barrier, hematoendoneurial barrier, peripheral neuropathy.

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Taxanes are a group of broad-spectrum chemotherapeutic agents which are highly effective [3, 9]; however, they have a negative impact on the peripheral nervous system [7, 14]. Paclitaxel (P) is one of the anti-neoplastic agents that affects the microtubules and prevents their depolarization resulting in abnormal intraneuronal transport. This is how most researchers explain peripheral neurotoxicity of P [6, 11]. It is a dose-dependent effect which manifests itself in most oncological patients treated with P as numbness, burning pain, paresthesia mainly in "gloves and socks" areas, joint and muscle pain, disordered motor function [8, 14]. Despite numerous studies, there are currently no effective neuroprotective schemes being able to significantly affect the clinical course of P-induced neuropathy. It is due to lack of knowledge of the pathomorphogenetic mechanisms of peripheral neuropathy which occur under the influence of the preparation. The overwhelming majority of research is limited to the study of qualitative and quantitative aspects of the damage to conducting component of the peripheral nerves since they are considered as the main ones in the development of P-induced peripheral neuropathy (PIPN) [4, 5]. Some authors indicated the possible role of the disorganization of connective tissue elements and the microcirculation system in the pathogenesis of PIPN; however, these issues were rarely considered in the context of the pathomorphogenesis in general [12]. Changes in nerve fibers of the sciatic nerve (SN) described in our previous studies, were accompanied by endoneurial edema of different severity degrees [1]. Therefore, particular attention has been paid to the study of the effect of P on the endoneurial capillaries as well as the perineurium of the SN under the influence of P.

Research purpose was to determine the patterns of structural and functional rearrangement of the components of the hematoendoneurial and the perineurial barriers of the SN in dynamics of experimental PIPN.

Materials and methods. Experiment was conducted on the random bred albino rats, weighing 150-200 g, that were divided into 3 groups. 35 animals of the 1st experimental group were administered