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MICROSCOPIC STRUCTURE AND THE PROCESS OF FORMATION OF MILKY SPOTS OF THE GREATER OMENTUM OF WHITE RATS

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To study the microscopic structure and the process of forming milky spots of the greater omentum of white rats, an experimental study was carried out on 15 male white rats of reproductive age, weighing 278.08 to 346.47 grams. The materials were preparations of the greater omentum, fixed in a 10 % neutral formalin solution, as well as total preparations stained with a hematoxylin-eosin solution. Milky spots of the greater omentum of white rats are presented as small lymphoid nodules of various shapes and sizes, which are orderly dispersed within the vascular-fatty arcades on the sides of the axial blood vessels. The smallest were located in the depth of the adipose tissue, adjacent to the axial vessels, and the largest were outside it. Along with them, there were also forms that occupy an intermediate position. All the main types of immunocompetent cells were concentrated in a certain order in the milky spots of the greater omentum.

Key words: greater omentum, milky spots, lymphoid nodules, lymphoid tissue, immunocompetent cells, mesothelial cells, adipocytes

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МІКРОСКОПІЧНА БУДОВА ТА ПРОЦЕС ФОРМУВАННЯ МОЛОЧНИХ ПЛЯМ ВЕЛИКОГО ЧЕПЦЯ БІЛИХ ЩУРІВ

З метою вивчення мікроскопічної будови та процесу формування молочних плям великого чепця білих щурів, проведено експериментальне дослідження 15 білих щурів-самців репродуктивного віку, масою від 278,08 до 346,47 грам. Матеріалом слугували препарати великого чепця, фіксовані в 10 % розчині нейтрального формаліну, а також тотальні препарати, забарвлені розчином гематоксиліну-еозину. Молочні плями у великому чепці білих щурів представлені у вигляді дрібних лімфоїдних вузликів, різної форми та величини, які впорядковано розосереджені в межах судинно-жирових аркад з боків осьових кровоносних судин. Найдрібніші знаходяться в товщі жирової тканини, примикаючи до осьових судин, а найбільші – за її межами. В молочних плямах великого чепця зосереджені в певному порядку всі основні типи імунокомпетентних клітин.

Ключові слова: великий чепець, молочні плями, лімфоїдні вузлики, лімфоїдна тканина, імунокомпетентні клітини, мезотеліальні клітини, адипоцити

The study is a fragment of the research project “Morphofunctional study of the internal organs of humans and laboratory animals in different aspects of the experimental medicine”, state registration No. 0121U108258.

The greater omentum is called the immune factory of the peritoneal cavity due to the higher number of antibodies in it as compared to the tissues of the spleen and liver [9, 12, 15].

The greater omentum of white rats, unlike other derivatives of the peritoneum, is its free extension from the greater curvature of the stomach to a certain depth of the peritoneal cavity, a duplication of the serous membrane, which is characterized by a composition of two interconnected structures. These structural elements are the so-called “vascular-fatty arcades”, which are associated with lymphoid nodules, known as milky spots with serous-reticular bridges that conjoin them [2, 14]. It has been established that milky spots appear in the middle of the embryonic period and exist until the end of life [9]. In adults, they are poorly distinguishable due to deposits of adipose tissue. The lymphoid tissue of the greater omentum in newborns is already up to 31.5 % of the total area of the organ. The maximum saturation of the greater omentum with lymphoid structures occurs in childhood, when up to 40–50 lymphoid nodules are determined per 1 cm^2 of the omental area and with an increase in life expectancy, the number of milky spots decreases [13, 15].

Immunological studies revealed that the omentum contains a large number of immunocompetent cells: macrophages, lymphocytes of various subpopulations. Cells, contained in milky spots, are distinguished into structural (fibroblasts, adipocytes, mesothelial and endothelial cells), functional (macrophages, stromal cells, high endothelial cells of venules) and migrating (lymphocytes, granulocytes, monocytes) [15].

The cells that make up the milky spot carry out phagocytosis of foreign structures, absorb bacteria, microparticles, and various dyes, and also synthesize antibodies [9, 12, 15].

Therefore, the omentum has the ability to cleanse the peritoneal cavity. It is believed that milky spots are also involved in the resorption of fluid in the peritoneal cavity [9, 12, 15].

Schurink B. et al. and Liu JY et al. described in detail the cellular structure of milky spots [11, 13], however, little is known about their development to date. To better understand the structure of milky spots in the greater omentum, it is necessary to study their histological structure and features of their formation. To the best of our knowledge, such studies of the stages of milky spots' formation process have not been published before. Therefore, the present study was carried out.

The purpose of the study was to establish the microscopic structure and the process of formation of milky spots of the greater omentum of white rats.

Materials and methods. 15 mature male white rats weighing 278.08 to 346.47 g were involved in the experiment. The material was the specimens of the greater omentum, fixed in 10 % neutral formalin solution, as well as whole mount, stained with hematoxylin and eosin. Before vivisection, all animals were kept under standard conditions of the experimental biological clinic (vivarium) of Poltava State Medical University, in compliance with the rules for keeping experimental animals established by the Directive of the European Parliament and Council (2010/63/EU), by the Order of the Ministry of Education and Science, Youth and Sports of Ukraine as of 01.03.2012 No. 249 "On the approval of the procedure for conducting experiments on animals by scientific institutions" and the "General ethical principles for animal experiments", adopted by the Fifth National Congress on Bioethics (Kyiv, 2013), (Minutes No. 198 as of 21.10. 2021 from the meeting of the Commission on Biomedical Ethics of the Poltava State Medical University) [3, 6]. After vivisection, which was carried out by the ether anesthesia overdose [8] in accordance with all the norms and requirements for conducting acute experiments on animals, in all animals, sequentially (on a dissecting device in the supine position of the animals), the abdominal cavity was dissected in a way to create a complete view of the internal organs in their natural relationships. Before the subsequent manipulations, at first, the entire contents of the peritoneal cavity were subjected to gentle washing with warm 0.9 % saline NaCl solution, and irrigation from a syringe with 10 % neutral formalin solution. Then, the whole mount of the greater omentum were extracted, and some of them were stained with hematoxylin and eosin solution.

The study was carried out using conventional histological methods for obtaining serial paraffin sections of 4 μm thick (Microm HM 325), which were stained with hematoxylin-eosin and Van Gieson's stain. The study and documentation were carried out using MBS-9, as well as in the "Konus" light microscope equipped with the Sigeta DCM-900 9.0MP digital microphotographic attachment with the Biorex 3 program adapted for these studies (serial number 5604). Morphometric characteristics of the tissue structures of the corresponding specimens were obtained using a system for visual analysis of histological specimens, as well as using the Sigeta X 1 mm/100 Div.x0.01 mm object- micrometer, the metric scale of which (equal to 1 mm, where the small division corresponds to 10 μm) was applied on the corresponding microphotograph obtained at an equivalent magnification [5].

Results of the study and their discussion. The findings of the study of the structural organization of the vascular-fatty arcades of the greater omentum have shown that lymphoid nodules in their rudimentary form appear among the adipocytes within individual lobular microvascular modules, which, in the process of their development, are gradually transformed with the changing conditions of the microenvironment, maintaining the same principle of association with the axial great vessels (Fig. 1 A, B).

Consequently, we hypothesize that the morphogenetic grounds for the development of structured lymphoid tissue in the greater omentum in the form of lymphoid nodules are individual lobules of their pre-formed adipose tissue, which creates the essential microenvironment for the colonization of precursor cells of T- and B-lymphocytes, as well as macrophages. The findings of the studies clearly show the main stages of the formation of milky spots. In our opinion, this process begins with the appearance of adipose lobules in some places (near the axial blood vessels) among adipocytes of limited aggregations (infiltrations) of lymphocytic elements, which gradually grow due to the assimilation of adipocytes (Fig. 2 A, B).

In this context, the word "assimilation" is justified, since individual adipocytes, being surrounded by lymphoid elements, are markedly diminished. Apparently, the process of the formation of milky spots is energy-consuming. Notably, these limited infiltrates of lymphoid cells are clustered near (or around) postcapillary venules, which can be considered quite understandable, since according to the basic provisions of microangiology, these capacitance microvessels are most adapted to diapedesis through their thin endothelial lining of the blood corpuscles.

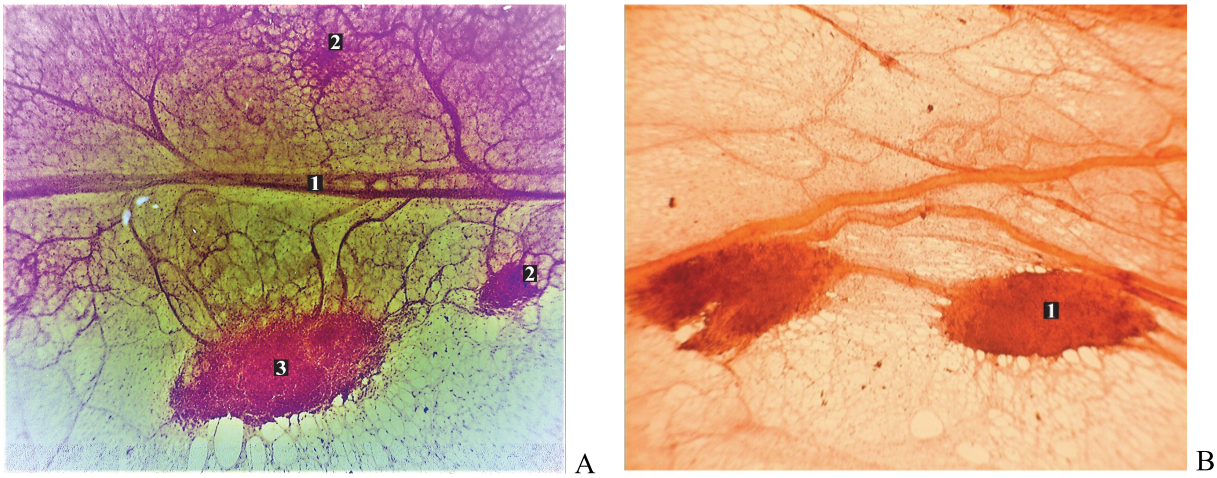

Fig. 1 A, B. Milky spots (lymphoid nodules) of the vascular-fatty arcades in the greater omentum of white rats. Whole mount; H&E stain. MBS-9 objective: 4$^{\times}$magnification. A: 1 – axial blood vessels; 2 – rudimentary forms of milky spots; 3 – definitive forms of milky spots. B: 1 – definitive forms of milky spots.

In addition to naive T- and B-lymphocytes, there are also monocytes among them, which, when they enter the perivascular zone, turn into macrophages, which become apparent in rudimentary milky spots among individual limited groups of lymphocytes.

The presence of individual plasma cells among them is not an exception, which can be identified at high magnifications of the microscope in the basophilic cytoplasm and the presence of cleared zone in it in the form of a "courtyard' (the location of the Golgi complex). The above structure of milky spots, at the rudimentary stages of their development, will serve as a key to deciphering the cytoarchitectonics of their mature definitive forms and explain the nature of the presence of basophilic granularity that is visible in the overall images, and some of them resemble mulberries in general appearance (Fig. 1 A, B).

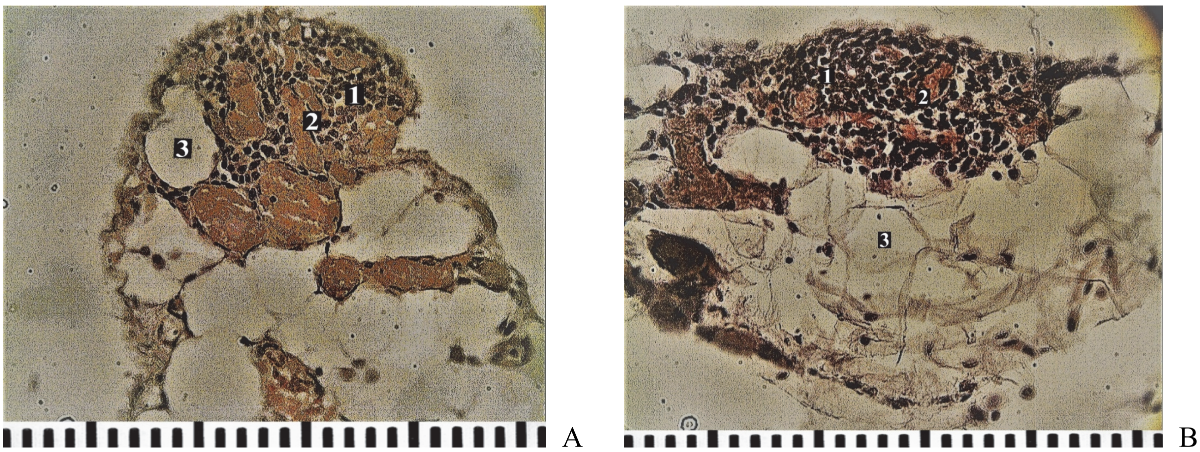

Fig. 2 A, B. Rudimentary forms of milky spots in the greater omentum of white rats. Paraffin sections; H&E stain; objective: 40$^{\times}$magnification. The smallest division in the metric scale is 10 µm. A: 1 – aggregation of lymphoid elements in the adipose lobuli; 2 – venous microvessels; 3 – adipocytes. B: 1 – aggregation of lymphoid elements in the adipose lobuli; 2 – venous microvessels; 3 – adipocytes.

On the histological sections, the shape of definitive milky spots mainly depends on a random angle of their section in the paraffin block. It has been found that on the transverse sections of the vascular-fatty arcades, they are covered with a serous membrane, consisting of mesothelium and underlying thin layer of loose fibrous connective tissue. A notable feature of this superficial zone of vascular-fatty arcades is the presence of small foci of lymphocytic infiltration, which are in close association with the mesothelium. We hypothesize that the so-called stigmata, through which the macrophages migrate into the peritoneal fluid, are located exactly in the above sites. However, no clear signs of the presence of such formations were found during the study.

In the cases where the sectional angle approximately coincides with the plane of the omentum, the shape of histological sections of milky spots approximately corresponds to their typical external, oblong ovoid shape (Fig. 3 A, B).

At first glance, in such presentation, the cytoarchitectonics of the definitive milky spot appears to be a chaotic, disordered aggregation of closely located lymphocytic elements, alternating with other tissue structures. However, in this chaos a certain order in the form of a convoluted distichous distribution of lymphoid cells, separated from each other by clear conformal gaps that belong to the labyrinth of the interstitial space can be distinguished.

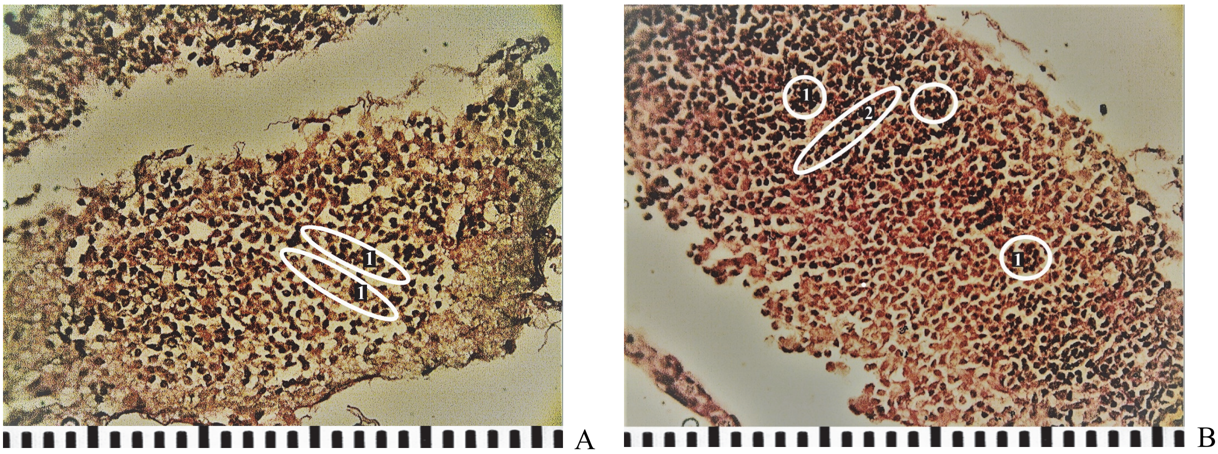

Fig. 3 A, B. Mature forms of milky spots in the longitudinal section of the vascular-fatty arcades of the greater omentum of white rats. Paraffin sections; Van Gieson's stain; objective: 40×magnification. The smallest division in the metric scale is 10 µm. A: 1 – two-row trajectories of lymphoid cells. B: 1 – glomerular forms of cooperation of lymphoid cells; 2 – two-row trajectories of lymphoid cells.

At the same time, these two-row lymphocytic trajectories form, in a regular fashion, microscopic lymphoid islands in the form of twists and glomeruli, varying in configuration (Fig. 4 A, B), which in their mass give the general appearance of milky spots basophilic granularity, which was noted above (Fig. 1 A, B).

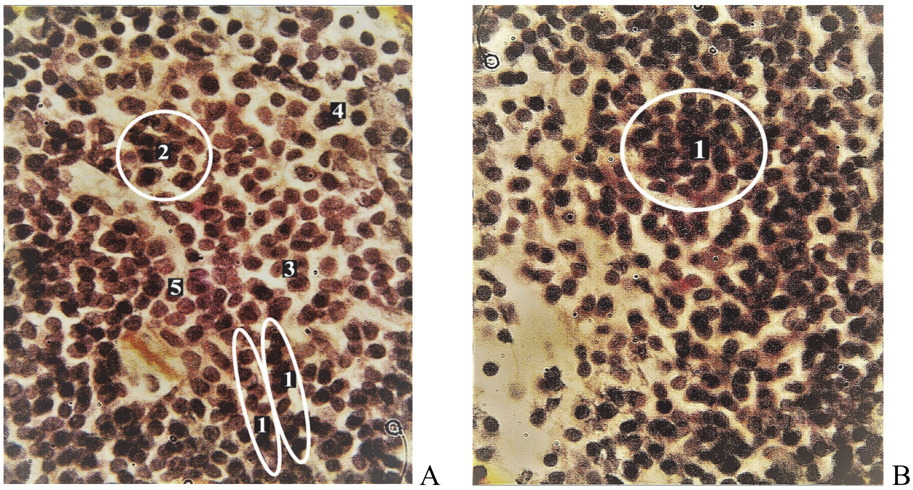

Fig. 4 A, B. Cytoarchitectonics of mature milky spots of the greater omentum of white rats. Paraffin sections; H&E stain; objective: 100×magnification. A: 1 – two-row trajectories of lymphoid cells; 2 – glomerular forms of cooperation of lymphoid cells; 3 – monocytes; 4 – macrophages; 5 – lymphocytes. B: 1 – glomerular forms of cooperation of lymphoid cells.

The findings of the study have established that the distribution of these microscopic lymphoid glomeruli is subject to the topology in the adipose lobules of postcapillary venules, which are the initial links at the first stages of milky spots' formation. From this point of view, the whole process can be considered as a sequential quantitative multiplication within the adipose lobules of focal infiltrations of immunocompetent cells and their consolidation into a single, territorially limited aggregation, which should be in concordance with the antigenic load of omentum at a given time.

Apparently, the greater omentum of white rats contains a well-developed lymphoid tissue, fragmented into separate structured aggregations, known as milky spots. This notion, in itself, does not reflect their true nature in terms of the place they occupy in the body's immune system. Most authors (including us) believe that milky spots belong to its peripheral part, which includes the lymph nodes, spleen, tonsils, as well as solitary and group lymphoid nodules (Peyer's patches) of the intestinal tract [7]. The question is whether milky spots are some kinds of special formations, or they are fundamentally structurally similar to other secondary immune organs, that is, to those in which the processes of antigen-dependent specialization and proliferation of lymphocytes occur [10]. If we carefully analyze the structural organization of the secondary immune organs, we can conclude that there is a fundamental similarity between them, consisting in the fact that they all represent a consolidation of structural and functional units, which are lymphoid nodules of the same type in structure (previously called follicles) which are similar to milky spots. That is, the latter are ordinary lymphoid nodules. However, if in the lymph nodes such formations are associated with lymphatic vessels, in the spleen – with blood vessels, in the tonsils – with the epithelium of the secondary crypts, and single and group lymphoid nodules of the intestine – with the intestinal epithelium, then milky spots, like lymphoid nodules, are functionally linked with mesothelium of the greater omentum. But unlike the lymphoid nodules of other secondary immune organs, milky spots have a morphogenetic relationship with adipose tissue [1]. Importantly, this is precisely what distinguishes them from similar structures of other peripheral organs of the immune system. In the publications this relationship has been mentioned as "fat-associated lymphoid clusters", which are described not only in the omentum and peritoneum, but also in other serous membranes, where visceral fat is usually deposited [4, 10].

When talking about the very natural essence of this inseparable connection, a very general concept is presented in the literature, according to which adipose tissue is a source of energy in the process of differentiation of certain populations of immunocompetent cells (mainly the regulatory T-lymphocytes), and on the other hand, it is considered that the lymphoid tissue of milky spots is involved in the homeostasis of visceral adipose tissue. If the second part of this concept can be considered acceptable to some extent, then the first judgment is not convincing, since in other secondary lymphoid organs the same process of differentiation of T-lymphocytes occurs without the participation of adipocytes.

It is known that stimulation of T-lymphocytes is carried out by means of antigen-presenting dendritic cells, the presence of which in the milky spots of the greater omentum, according to the literature, is controversial [11, 12, 13, 15].

Unfortunately, we do not currently have our own decisive data in this respect. But free macrophages, contained in sufficient quantities in milky spots, can also present antigens to immunocompetent cells. They can easily migrate from milky spots (through stigmata in the mesothelium) into the peritoneal fluid, from where, after absorbing a foreign agent, they return back, presenting it to naive T-lymphocytes, which in turn trigger the corresponding immune responses through B-lymphocytes. These cooperative intercellular interactions occur in the lymphoid glomeruli around postcapillary venules. Eventually, all the main types of immunocompetent cells are concentrated in a certain order in the milky spots of the greater omentum, but it has not yet been established whether they have separate T-dependent and B-dependent zones. Importantly, in the process of immunization of milky spots, mesothelial cells, covering them on both sides, are also involved, which along the edges of the vascular-fatty arcades, consolidating with each other, pass into the intermediate zones of the greater omentum.

Conclusions

1. Milky spots of the greater omentum of white rats are presented as small lymphoid nodules of various shapes and sizes, which are orderly dispersed within the vascular-fatty arcades on the sides of the axial blood vessels. The smallest are located in the depth of the adipose tissue, adjacent to the axial vessels, and the largest are outside it. Along with them, there are also forms that occupy an intermediate position. In our opinion, this picture demonstrates the process of development of lymphoid nodules.

2. This process begins with the emergence of lymphoid nodules in separate lobules of adipose tissue near the axial blood vessels. Subsequently, they, gradually becoming larger, move beyond the vascular-fatty arcades, thus becoming mature, definitive forms that correspond to the name of the milky spots. But in their internal cytoarchitectonics, they should be considered as typical lymphoid nodules belonging to the structures of the peripheral part of the immune system, which, unlike other similar formations, are associated with the mesothelium and, in the process of their development, are closely associated with adipose tissue.

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EFFECT OF LONG-TERM USE OF PROTON PUMP INHIBITORS ON THE CONTENT OF NITRITE IONS IN THE BLOOD SERUM AND MUCOUS COATING OF THE GASTROINTESTINAL TRACT OF RATS

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The purpose of the study was to determine the content of nitrite ions in blood serum and mucous membranes of the stomach and colon in rats under the conditions of long-term use of proton pump inhibitors Omeprazole and Pantoprazole. The study was performed on 30 white non-linear male rats, divided into three groups. The control (first group) received water for injections intraperitoneally once a day for 28 days. The second – Omeprazole. The third – Pantoprazole. After long-term administration of omeprazole and pantoprazole, the concentration of NO^{2-} in blood serum increased by 24 % ($p<0.05$) and 13 % compared to the control group. The increase in the concentration of NO^{2-} in the mucous membranes of the stomach and colon after 28-day suppression of HCl secretion in the stomach by Omeprazole and Pantoprazole was much more pronounced and amounted in the stomach to 144 % ($p<0.05$) and 85 % ($p<0.05$) more compared to the control group. In the mucous membrane of the large intestine, it was 159 % ($p<0.05$) and 119 % more than in the control group. Long-term inhibition of hydrochloric acid secretion in the stomach of rats by proton pump blockers Omeprazole and Pantoprazole caused excessive generation of nitric oxide in blood serum and mucous membranes of the digestive tract of rats. The negative effect of pantoprazole was less pronounced than that of omeprazole.

Key words: hypochlorhydria, pantoprazole, omeprazole, inflammatory process.

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ВПЛИВ ТРИВАЛОГО ЗАСТОСУВАННЯ ІНГІБІТОРІВ ПРОТОННОЇ ПОМПИ НА ВМІСТ НІТРИТ-ІОНІВ У СИРОВАТЦІ КРОВІ ТА СЛИЗОВІЙ ОБОЛОНЦІ ШЛУНКОВО-КИШКОВОГО ТРАКТУ ЩУРІВ

Метою дослідження було визначити вміст нітрит-іонів у сироватці крові та слизових оболонках шлунку та товстої кишки щурів за умов тривалого застосування інгібіторів протонної помпи омепразолу та пантопразолу. Дослідження проводили на 30 білих нелінійних щурах-самцях, розділених на три групи. Контроль (перша група) отримував воду для ін'єкцій внутрішньочеревно 1 раз на добу протягом 28 днів. Другий – Омепразол. Третій – Пантопразол. Після тривалого застосування омепразолу та пантопразолу концентрація NO2- у сироватці крові зросла на 24 % ($p<0,05$) та на 13 % порівняно з контрольною групою. Підвищення концентрації NO2- у слизових оболонках шлунка та товстої кишки після 28-денного пригнічення секреції HCl у шлунку омепразолом та пантопразолом було значно більш вираженим і становило у шлунку 144 % ($p<0,05$) та на 85 % ($p<0,05$) більше порівняно з контрольною групою. У слизовій оболонці товстого кишечника він становив на 159 % ($p<0,05$) і на 119 % більше, ніж у контрольній групі. Тривале пригнічення секреції соляної кислоти в шлунку щурів блокаторами протонної помпи омепразолом і пантопразолом викликало надмірне утворення оксиду азоту в сироватці крові та слизових оболонках травного тракту щурів. Негативний ефект пантопразолу був менш вираженим, ніж омепразолу.

Ключові слова: гіпохлоргідрія, пантопразол, омепразол, запальний процес.

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Proton pump blockers contribute to bacterial overgrowth in every part of the digestive tract [3], as well as hypergastrinemia [9].

Prolonged hypergastrinemia and bacterial imbalance disrupt digestive motility, adversely affecting the ability to evacuate through the intestines [4, 10]. This leads to the development of a chronic inflammatory process in the intestines due to conflicting motor functions and bacterial imbalance [2].