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AGE CHARACTERISTICS OF MELATONIN 1A RECEPTORS' DENSITY IN NEURONS OF THE ANTERIO-LATERAL PREOPTIC NUCLEUS OF RATS' HYPOTHALAMUS UNDER LIGHT STIMULATION AND ADMINISTRATION OF MELATONIN

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The article provides a comparative analysis of the results of an immunohistochemical study of the melatonin type 1A receptors' density in the neurons of the anterolateral preoptic nucleus of the hypothalamus in mature and old rats. It was established that daily fluctuations in the density of the studied structures are subject to circadian rhythms, with the highest values at 2 a.m., while at 2 p.m. it decreases. In old rats, the density of melatonin type 1A receptors in neurons of the anterolateral preoptic nucleus of the hypothalamus is lower than in mature rats. Light stimulation leads to desynchronization and decreased density of melatonin 1A receptors in both mature and aged rats. When using exogenous melatonin in the dose of 0.5 mg/kg against the background of long-term lighting, a probable increase in the mean density of melatonin 1A receptors in neurons of the anterior-lateral preoptic nucleus of the hypothalamus was observed.

Key words: sleep-wake cycle, anterolateral preoptic nucleus of the hypothalamus, chronorhythms, lighting, melatonin.

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ВІКОВІ ОСОБЛИВОСТІ ЩІЛЬНОСТІ МЕЛАТОНІНОВИХ РЕЦЕПТОРІВ 1А У НЕЙРОНАХ ПЕРЕДНЬО-БІЧНОГО ПЕРЕДЗОРОВОГО ЯДРА ГІПОТАЛАМУСА ЩУРІВ ЗА СВІТЛОВОЇ СТИМУЛЯЦІЇ ТА УВЕДЕННЯ МЕЛАТОНІНУ

У статті наводиться порівняльний аналіз результатів імуногістохімічного дослідження щільності рецепторів до мелатоніну типу 1А в нейронах передньо-бічного передзорового ядра гіпоталамуса зрілих і старих щурів. Встановлено, що добові коливання щільності досліджуваних структур підпорядковуються циркадіанним ритмам, з найвищими показниками о 02.00 год., тоді як о 14.00 год. вона знижується. У старих щурів щільність рецепторів до мелатоніну типу 1А у нейронах передньо-бічного передзорового ядра гіпоталамуса є нижчою ніж у зрілих. Світлова стимуляція призводить до десинхронізації та зниження щільності рецепторів до мелатоніну 1А як у зрілих, так і у старих щурів. При застосуванні екзогенного мелатоніну в дозі 0,5 мг/кг на тлі тривалого освітлення спостерігали вірогідне підвищення середніх величин щільності рецепторів до мелатоніну 1А у нейронах передньо-бічного передзорового ядра гіпоталамуса.

Ключові слова: цикл сон-неспанья, передньо-бічне передзорове ядро гіпоталамуса, хроноритми, освітлення, мелатонін.

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An integral and fundamental property of all living organisms are biological rhythms [12], which play an important role in adaptation and survival in the environment. [10]. The most important are circadian rhythms, which belong to free-flowing endogenous rhythms, lasting approximately 24 hours, which are directly related to the cyclical change in illumination, that is, the rotation of the Earth around its axis. Circadian rhythms of motor activity, body and skin temperature, pulse and breathing rates, blood pressure, diuresis, etc. have been established [3].

Our 24-hour sleep-wake cycle is the most obvious circadian rhythm observed in humans and many animals, but sleep is more than just part of the circadian system [5]. People spend about a third of their lives in sleep, and its quality determines the overall level of health. Sleep is a very complex physiological process that requires the interaction of different areas of the brain [7]. Sleep consists of two phases, namely the phase of slow sleep, in which 4 stages are distinguished: the 1st stage – dozing, the 2nd stage – light sleep, the 3rd stage – moderately deep sleep and the 4th stage – deep sleep and phases of rapid eye movement sleep. The entire night's sleep consists of 4–5 such cycles, each of which begins with the first stages of slow sleep and ends with the phase of rapid sleep. Each human cycle lasts about 90–100 minutes [3]. Healthy sleep performs restorative functions in relation to the brain and the body as a whole [1].

The key role in the regulation of the sleep-wake cycle is played by the anterior-lateral preoptic nucleus, which is located in the anterior hypothalamus [3]. About 85 % of the neurons of this nucleus contain the inhibitory neurotransmitters galanin and gamma-aminobutyric acid and provide innervation of the main monoamine systems of the brain, which determine the period of wakefulness [9].

Another important structure involved in the regulation of the sleep-wake cycle is the pineal gland, which synthesizes the hormone melatonin [6]. The rhythm of melatonin production has a clear circadian character: its concentration in the blood during the dark part of the day is 5–10 times higher than during the day: in the evening, the level begins to rise, reaching a maximum – from 60 to 100 mg/ml – at 2–4 a.m., and then gradually decreases and from 7 a.m. to 8 p.m. remains low – below 20 mg/ml [4]. The circadian rhythm of melatonin secretion is necessary to regulate the normal sleep-wake cycle, which is important for optimal health [15]. In the process of aging, the circadian rhythm of melatonin secretion is preserved, but its mean daily concentration in the elderly is by 50 % lower than in the young. With aging, the sleep mode also changes, in particular, this is manifested by a decrease in total sleep time [11]. The circadian rhythm is important for the optimal functioning of our body, and disturbances in the sleep-wake cycle lead to psychiatric and neurodegenerative diseases, cognitive and metabolic disorders, weakened immunity, increased risk of oncological and cardiovascular diseases, and premature death [13]. To solve all these problems, a necessary condition is the study of the fundamental mechanisms of sleep-wake cycle regulation. The presence of melatonin receptors in the anterior-lateral preoptic nucleus of the hypothalamus is a convincing criterion for the participation of this nucleus in temporal organization.

The purpose of the study was to investigate the effect of light stimulation and melatonin administration on the density of melatonin type 1A receptors in neurons of the anterolateral preoptic nucleus of the hypothalamus in mature and old rats.

Materials and methods. Experiments were carried out on sexually mature and old white non-linear male rats. Experimental animals were divided into six groups, each of which, in turn, consisted of two subgroups (six animals each). The first group – mature rats, which were kept for seven days in the conditions of a standard lighting regime (illumination from 8 a.m. to 8 p.m. using fluorescent lamps, illumination level – 500 lux). The second group – mature rats, which during the same period, were in conditions of round-the-clock lighting (light stimulation).

The third group – mature rats, which were injected intraperitoneally with melatonin (Sigma, USA) at the dose of 0.5 mg/kg of the rat's body weight for seven days against the background of round-the-clock lighting. The fourth group – old rats kept under a standard light regime (the same conditions as for mature rats). The fifth group – old rats, which were under 24-hour lighting (light stimulation) for seven days. The sixth group – old rats, which were injected intraperitoneally with melatonin (Sigma, USA) at the dose of 0.5 mg/kg body weight of the rat for 7 days against the background of round-the-clock lighting.

To detect circadian differences in the density of type 1A melatonin receptors at the end of the seven-day experiment, the next day at 2 p.m. and 2 a.m., the animals were sacrificed by performing one-moment decapitation under ethanol anesthesia (40.0 mg/kg, intraperitoneally). All stages of the experiment were carried out in compliance with the main provisions of the Resolution of the First National Congress on Bioethics "General Ethical Principles of Animal Experiments" (2001), the Convention of the Council of Europe on the Protection of Vertebrate Animals Used in Experiments and Other Scientific Purposes (dated 18.03.1986), EEC Directive No. 609 (dated 24.11.1986) and Orders of the Ministry of Health of Ukraine No. 690 of 23.09.2009, No. 944 dated 14.12.2009, No. 616 of 03.08.2012 and the laws of Ukraine.

The removed brain was fixed in a neutral buffered 10 % formalin solution for 22–24 hours. Before immersion in the formalin solution, small incisions were made in the soft shell of the brain for better impregnation of the brain tissues with formalin. Next, slices about one millimeter thick were sliced from the fixed rat brain tissue, with the first slice passing through the anterior part of the optic nerve junction, and the second slice passing through the posterior part of the optic nerve junction. The cut plates of brain tissue were dehydrated in an ascending battery of alcohols and embedded in paraffin at 58°C. Serial histological sections with a thickness of 5 µm were made on a sled microtome. Further, immunohistochemical techniques were performed on the sections in accordance with the protocols provided by the manufacturer. In particular, primary antibodies against type 1A melatonin receptors (Abcam) were used. Visualization of primary antibodies was performed with the Dako polymer system with diaminobenzidine dye (gives a brown color to the locations of the studied antigens) using a Delta Optical Evolution 100 microscope (planachromatic lenses) and an Olympus SP550UZ digital camera.

On digital copies of images, the intensity of staining was assessed by computer microdensitometry. To do this, using a licensed copy of the computer ImageJ v1.48 software, the computer value of the staining

brightness was first obtained by the microprobe method in the 8-bit analysis system, and then these values were converted into the value of the relative optical density by means of a logarithmic transformation (in opt.density units), in the range from 0 (absolute transparency) to 1 (absolute opacity).

Statistical processing of the results was carried out using a licensed copy of the PAST computer software. A preliminary test for the normality of the distribution was applied according to the Wilkie-Hahn-Shapiro test. For all statistical samples, according to this criterion, the hypothesis of distribution normality was not rejected, therefore parametric methods of statistical analysis were used: calculation of the arithmetic mean and its error ($M \pm m$), odd two-sided Student's test. At the same time, taking into account the relatively small number of statistical samples, the Mann-Whitney test was additionally applied to increase the reliability of the testing results calculating differences between the research groups in the mean trends.

Results of the study and their discussion. Specific immunohistochemical staining for melatonin type 1A receptors could be observed in all neurons of the anterolateral preoptic nucleus of the hypothalamus, regardless of their localization in the nucleus. The staining was mostly fine-grained or almost diffuse in nature and covered the membrane of neurons and their cytoplasm. Observing the intensity of immunohistochemical staining from one neuron to another, it can be stated that it had different strength both in relation to the membrane and in relation to the cytoplasm.

There were neurons with both strong staining and moderate or even weak staining, therefore all measurements of the specific staining optical density for type 1A melatonin receptors in neurons of the anterolateral preoptic nucleus of the hypothalamus were performed on the cytoplasm of cells where the staining was stable. Mean indices of the staining optical density for type 1A receptors' melatonin of neurons of the anterior-lateral preoptic nucleus of the hypothalamus at 2 p.m. and 2 a.m. are indicated in Table 1.

Table 1

Optical density of specific staining for type 1A melatonin receptors in neurons of the anterolateral preoptic hypothalamic nuclei of rats ($M \pm m$)

Time of the day	Optical density of immunohistochemical staining on melatonin 1A receptors (optical density units)	
	Mature rats	Old rats
2 p.m.	0.248±0.0018	0.211±0.0014 ($p_2 < 0.001$)
2 a.m.	0.264±0.0016 ($p_1 < 0.001$)	0.216±0.0013 ($p_1 < 0.05$) ($p_2 < 0.001$)

Note: p_1 is the probability of a difference compared to the previous time interval; p_2 is the probability of a difference compared to another study group.

From the data in Table 1, it can be seen that the optical density of staining for type 1A melatonin receptors in the neurons of the anterolateral preoptic nucleus of the hypothalamus of mature rats (Fig. 1) is always greater than that of old rats (Fig. 2).

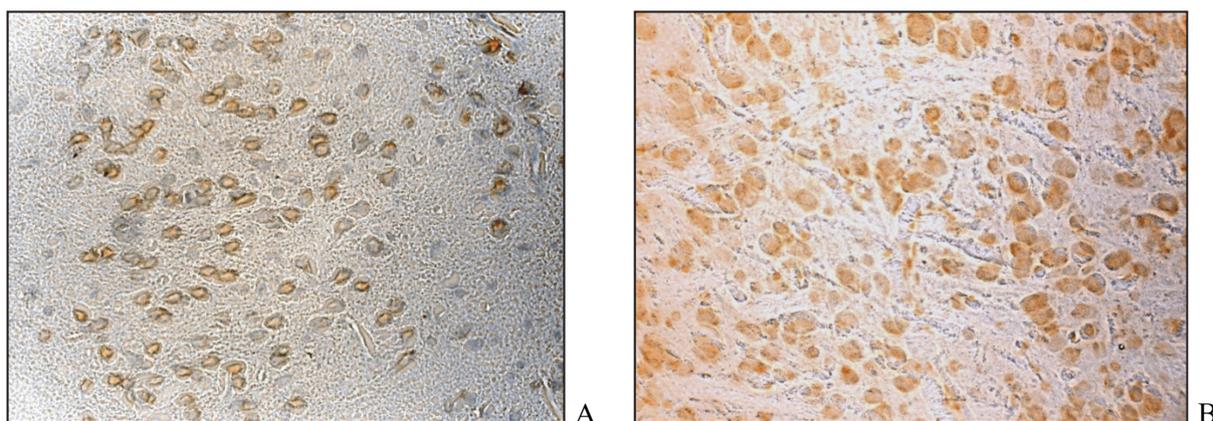


Fig. 1. Neurons of the anterolateral preoptic nucleus of the hypothalamus in a mature rat at 2 p.m. (A) and at 2 a.m. (B) using immunohistochemical methods for type 1A melatonin receptors. About. x20. OK. x10 (optical magnification x200).

At the same time, in mature rats, the optical density of staining for melatonin 1A receptors in the neurons of the anterior-lateral preoptic nucleus of the hypothalamus for the period of the day 2 a.m. on average, it is higher than at 2 p.m., while in old rats, such a regularity is not noted. In old rats, despite the lower mean values of the optical density of specific staining for melatonin receptors 1A in the neurons of the anterior-lateral preoptic nucleus of the hypothalamus, it was still possible to notice sufficiently intense staining in individual neurons.

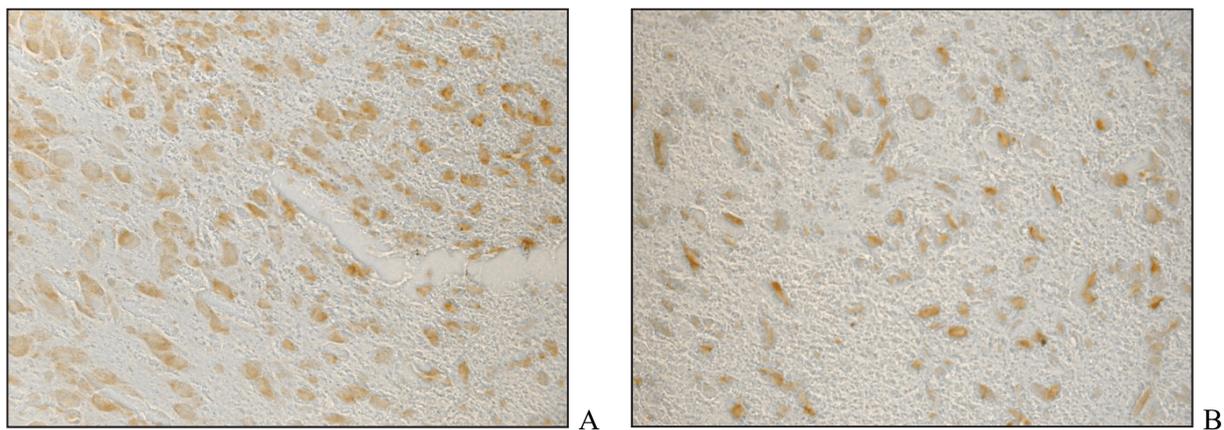


Fig. 2. Neurons of the anterior-lateral preoptic nucleus of the hypothalamus in an old rat at 2 p.m. (A) and at 2 a.m. (B) using the immunohistochemical method for type 1A melatonin receptors. xOb. 20 xOk.10 (optical magnification x200).

Under the conditions of light stimulation, the intensity of the specific staining optical density for type 1A melatonin receptors in the neurons of the anterior-lateral preoptic nucleus of the hypothalamus sharply decreased, which was visible from the optical density of staining (Table 2).

Table 2

Optical density of specific staining for type 1A melatonin receptors in neurons of the anterolateral preoptic hypothalamic nuclei of rats under conditions of light stimulation (M ± m)

Time of the day	Optical density of immunohistochemical staining on melatonin 1A receptors (optical density units)	
	Mature rats	Old rats
2 p.m.	0.180±0.0018	0.148±0.0013 (p ₂ <0.001)
2 a.m.	0.182±0.0017 (p ₁ >0.05)	0.132±0.0012 (p ₁ <0.001) (p ₂ <0.001)

Note: p₁ is the probability of a difference compared to the previous time interval; p₂ is the probability of a difference compared to another study group.

This occurred both in mature and old rats, in the latter the decrease was particularly significant. It is worth noting that in mature rats no differences were registered in the mean trends between the optical density of specific staining in the neurons of the anterolateral preoptic nucleus of the hypothalamus between the study periods of 2 a.m. and 2 p.m., while in old rats, the intensity at 2 a.m. is paradoxically smaller than at 2 p.m.

Administration of melatonin to rats kept under conditions of light stimulation led to an increase in the mean values of the optical density of specific staining for type 1A melatonin receptors in neurons of the anterolateral preoptic nucleus of the hypothalamus at 2 a.m. and 2 p.m. both in mature and old rats (Fig. 3).

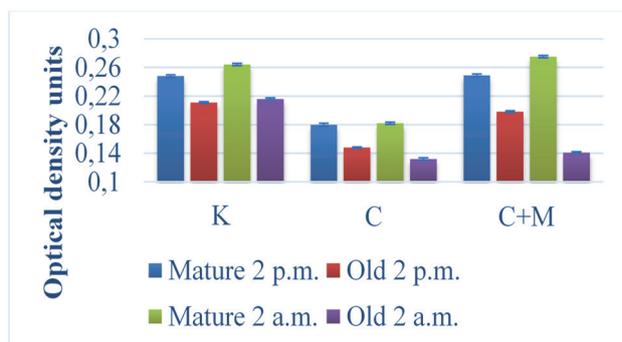


Fig. 3. Optical density of immunohistochemical staining for type 1A melatonin receptors in neurons of the anterolateral preoptic nucleus of the hypothalamus in mature and old rats under standard and 24-hour lighting and melatonin administration (in units of optical density). K – control, C – light stimulation, C+M – administration of melatonin against the background of light stimulation.

anterolateral preoptic nucleus of the hypothalamus made at 2 a.m. – 0.198±0.0013 units of optical density, at 2 p.m. – 0.141±0.0010 units of optical density.

The optical density increased more significantly in mature rats, in particular, at 2 p.m. – to the level of rats that were kept under a normal light regime (0.249±0.0017 units of optical density), and at 2 a.m. – even higher than the indices of rats that were kept under a normal light regime (0.275±0.0015 units of optical density). In old rats, an increase in the mean value of the optical density of specific staining for type 1A melatonin receptors in the neurons of the anterolateral preoptic nucleus of the hypothalamus was probable (p<0.001), but it was impossible to reach the mean level in rats kept under the usual light regime either at 2 a.m. or at 2 p.m. Data on the optical density of type 1A melatonin receptors in the neurons of the

Thus, we established many dependencies between the time of day, the lighting regime, and the density of type 1A melatonin receptors in the neurons of the anterolateral preoptic nucleus of the hypothalamus. In particular, daily fluctuations of the optical density (density) of type 1A melatonin receptors in the neurons of the anterior-lateral preoptic nucleus of the hypothalamus are characterized by a clear circadian rhythm, with the highest values at 2 a.m., while at 2 p.m. it decreases ($p < 0.001$).

It is also important to note that with age, the number of melatonin receptors in organs and tissues decreases [14], which is also proven by the results of our studies. In old rats, the density of type 1A melatonin receptors in neurons of the anterolateral preoptic nucleus of the hypothalamus is lower than in mature animals ($p < 0.001$). This may be associated with a decrease in the total number of pinealocytes, the development of the pineal gland sclerosis and, as a result, a decrease in the concentration of melatonin with age [2].

Light stimulation leads to a decrease in the density of type 1A melatonin receptors in neurons of the anterolateral preoptic nucleus of the hypothalamus in mature and old rats. However, if the circadian rhythm of the studied structures under the conditions of light stimulation is preserved in mature rats, then the density intensity of type 1A melatonin receptors in old rats at 2 a.m. is paradoxically smaller than at 2 p.m.

Melatonin at a dose of 0.5 $\mu\text{g}/\text{kg}$ of animal body weight was used to correct the detected deviations in the density of type 1A melatonin receptors caused by prolonged exposure of rats to light [8]. With the introduction of exogenous melatonin against the background of constant lighting, a probable ($p < 0.001$) increase in the mean density of type 1A melatonin receptors in the neurons of the anterolateral preoptic nucleus of the hypothalamus, compared to animals that were not injected with the drug against the background of light stress. However, in old rats, it was impossible to reach the level of animals kept under the standard lighting regime neither at 2 a.m. nor at 2 p.m., which can be associated with a decrease in compensatory capabilities of the body in old rats.

Conclusions

1. The density of melatonin type 1A receptors in the neurons of the anterolateral preoptic nucleus of the hypothalamus is characterized by a clear circadian rhythm, with the highest values at 2 a.m., while it decreases at 2 p.m.

2. In old rats, the density of melatonin type 1A receptors in neurons of the anterolateral preoptic nucleus of the hypothalamus is lower than in mature rats.

3. Light stimulation leads to a violation of the circadian rhythm and a decrease in the density of melatonin 1A receptors in the neurons of the anterolateral preoptic nucleus of the hypothalamus in mature and old rats. However, in old rats, the intensity of the melatonin 1A receptors' density at 2 a.m. is paradoxically lower than at 2 p.m.

4. Administration of exogenous melatonin at a dose of 0.5 mg/kg leads to a probable increase in the mean density of melatonin type 1A receptors in the neurons of the anterior-lateral preoptic nucleus of the hypothalamus.

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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 кровонесних 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

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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 cm² of the omental area and with an increase in life expectancy, the number of milky spots decreases [13, 15].