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ULTRASTRUCTURAL CHANGES IN THE ORGANS OF THE IMMUNE SYSTEM UNDER THE INFLUENCE OF XENOBIOTICS

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Development of human civilization since the XX century is undoubtedly connected with more efficient food distribution chaining processes as chronic lack of time in highly developed societies resulted in changes in their lifestyles and in patterns of consumption [17]. Migration from FCM might be the largest source of food contamination in terms of amount as well as the number of substances. Nonetheless, maybe because of its complexity, but also the little alerting character (clean-looking materials, no intention of being toxic like pesticides), it was not given corresponding weight for a long time [7].

Nowadays scientific achievements in various areas of lives have caused the creation of more and more «foreign body substances» known as xenobiotics. Different chemical have the detrimental effect on the body systems and, thus, all humanity. Diverse xenobiotics have an immuno-suppressive effect and, therefore, the organism becomes responsive to viral, bacterial and parasitic diseases [5]. Exposure to environmental contaminants can produce profound effects on the immune system. Many different classes of xenobiotics can significantly suppress or enhance immune responsiveness depending on the levels (i.e. dose) and context (i.e. timing, route) of exposure [8]. The immune system reacts sensitively to a concentration of chemical substances that are not yet toxic to other systems of the organism [6]. Understanding how environmental contaminants impact immune responsiveness not only helps in the effective regulation of pollutants and improving public health, but also provides novel insights into basic functions of the immune system [8].

The immune system plays a crucial role in maintaining health; however, accumulating evidence indicates that this system can be the target for immunotoxic effects caused by a variety of chemicals including the environmental pollutants. The thymus and spleen are primary lymphoid organ that manifests dynamic physiological changes as animal age in addition to being exquisitely sensitive to stress and toxic insult [6, 13] with the first lymphoid tissue to respond to immunotoxic xenobiotics in that organs usually.

One of xenobiotics type is class of polyethers belonging to the group called “Laproxides”, which are used in various sectors of the economy for the obtaining plastics, epoxy resins, lacquers, enamels, adhesives, etc. For the present research widely used polyether – tryglycidyl ether of polyoxypropylenetriol (TEPPT) [2,12] with molecular weight 303 (L-303) was chosen. Manufactures based on polyethers are used in machine-building, radio engineering, pharmaceutical, chemical, aviation, automotive and

other branches of the national economy. The choice of this group of substances was performed due to large volumes of production, extensive contact with the population, the lack of prognostic characteristics of their potential danger for humans and warm-blooded animals, and the need to justify pathological mechanisms of structural and metabolic disorders under prolonged intake of subtoxic doses. As it is widely accepted that human health is a product of both genetics and the environment; a premise that also holds true for the immune system [8] with unclear morphogenetic aspect we select the purpose of our work as detection of ultrastructural changes in the spleen and thymus under the influence of tryglycidyl ether of polyoxypropylenetriol and propylene glycol.

Material and methods. Experimental work was performed as a part of the research topic of the Human Anatomy department of the Kharkiv National Medical University «Morphological features of the organs and systems of the human body at the stages of ontogenesis”, (number of the state registration 0114U003388) as we described before [2]. The study was performed on 72 outbred WAG male matured rats with the weight 200 ± 10 g. The control and experimental series consisted of animals of the same age. Animals were divided into 2 series. The first seria - control animals (3 groups, 8 animals in each), were fed a regular diet and received an appropriate amount of water. The second seria was experimental animals. They were randomly divided into 3 groups 8 in each depending on the dose of induced polyether and duration of administration: 7 days, 15 days, 30 days and 45 days. All laboratory animals were maintained in the conventional environment of Kharkiv National Medical University vivarium in a controlled-temperature room $20\pm 2^{\circ}\text{C}$, humidity $65\pm 10\%$. All rats were treated via gastric gavage during 7, 15, 30, 45 days by aqueous solutions of TEPPT and propylene glycol (PP) in the doses 1/10 and 1/100 LD50 in conversion to 5.75 g/kg and 26.38 g/kg. At the end of the investigation, changes were observed. Food intake and body weight were measured every 2 days. All rodents were deduced from the experiment by immediate cervical dislocation according to European Convention for the Protection of Vertebrate Animals (Strasbourg, 18.03.1986), principles of Ukrainian law №3447-IV about the protection of animals from cruel treatment.

Ultramicroscopic examination of the spleen and thymus has been performed also. For electron microscopic examination immediately after removing a pieces of spleen and thymus with a volume of 1 mm³ were immersed in a glutaraldehyde fixator according to M.Karnovsky for 24

hours. After this, the material was kept in 1% osmium tetroxide according to G.Palade for 1 hour, dehydrated in ethanol of increasing concentration and absolute acetone, poured with a mixture of epoxy resins (epon-araldit). Polymerization was carried out for 36 hours at 60°C. Ultrathin sections 0.5 μm thickness were made on ultramicrotome UMTF-4 of Sumy Electron factory (Ukraine), contrasted in a solution of uranyl acetate and lead citrate according to E.Reynolds and investigated in an electron microscope EM-125 with the following photographing. Part of obtained material was fixed in 10% neutral buffered formalin for 24 hours, were subjected to standard proceeding and embedded in paraffin. From the prepared blocks made serial sections thick 5×10^{-6} m. Slides were stained with hematoxylin and eosin (H&E) [2]. Histological examination of removed spleens was performed according to accepted guidelines with microscope «Olympus BX41» followed by morphometric study using «Olympus DP-soft 3.12» program. All values are expressed as means, standard deviation and standard error of the mean for statistical analysis. Statistical comparison was performed using Mann-Whitney test for statistical analysis [11]. The accepted level of significance was $p \leq 0.05$.

Results and their discussion. We described the received and analyzed data about macroscopical and histological changes of spleen under TEPPT influence in previous work [2]. We detected that The spleen is very sensitive to the effects of xenobiotics.

In rats after the administration of TEPPT, white pulp of spleen is represented by periarterial lymphoid follicles occasionally containing germinal centers (Fig. 1b). The diameter of the lymph follicles is statistically significantly different with the control data from 7th day, in later observation periods the indices become smaller than in the control groups [2]. The germinal centers of the lymph nodes in the early periods of observation are visualized only in single lymphatic follicles. Their diameter is smaller than in groups of control animals. The parameters of the width of the mantle and marginal zones of lymphatic follicles are also reduced in comparison with the control. The central arteries of lymphatic follicles have thicker walls due to the development of sclerotic changes. Trabecular connective tissue is well defined, its thickness is increased. Morphometric data prove that TEPPT is even reflected in histological features (reliable changes of the of the white pulp area of the spleen from $17.87 \pm 1.04\%$ to $27.37 \pm 1.71\%$, diameter of lymphatic follicles from $426.59 \pm 11.18 \mu\text{m}$ to $382.31 \pm 11.73 \mu\text{m}$, width of the mantle zone from $45.73 \pm 1.08 \mu\text{m}$ to $37.18 \pm 2.29 \mu\text{m}$, width of the marginal zone from $81.32 \pm 1.79 \mu\text{m}$ to $74.63 \pm 2.08 \mu\text{m}$, width of the periarterial zone from $88.73 \pm 2.69 \mu\text{m}$ to $97.24 \pm 2.61 \mu\text{m}$) [2].

The cellular composition of the white pulp of the spleen is represented by small, medium and large lymphocytes, plasmocytes, and macrophages, but small forms of lymphocytes predominate. There are cells of the my-

eloid sprout series: neutrophilic, eosinophilic, basophilic granulocytes and erythrocytes.

Large, rounded nuclei of small lymphocytes are evenly surrounded by a narrow rim of the cytoplasm in control group (Fig. 1a). The nuclei are dominated by compact heterochromatin, which belongs to the inner nuclear membrane in the form of a wide girdle, passing into centrally located clumps, between which is a diffuse euchromatin. Margination of chromatin has been observed. Nuclei often have invaginations of karyolemma, sometimes they contain nucleolus, dilatation of mitochondria (Fig. 1c-f).

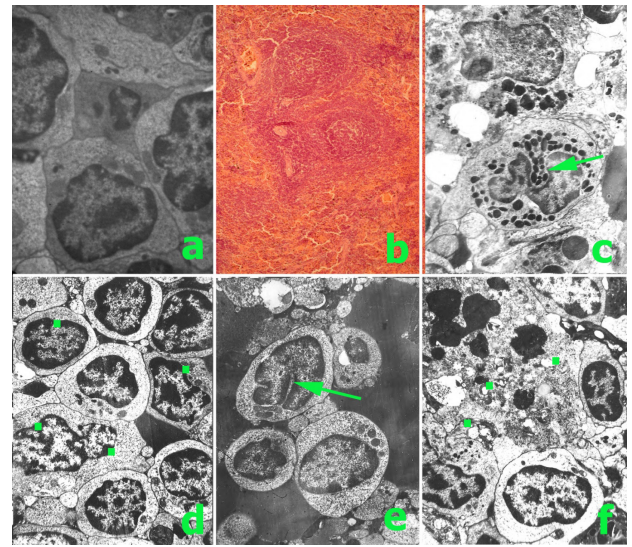


Fig. 1. Electron microscopy of spleen from control group, magnification $\times 8000$ (a); Histological structure of spleen after 45 days of treating by solutions of TEPPT in the dose $1/10 LD_{50}$, H&E stain, magnification $\times 100$ (b); Ultrastructural changes in spleen under influence of xenobiotics with diffuse euchromatin in nuclei, appearance of pronounced invaginations of karyolemma (arrows), condensed, wrinkled cytoplasm, chromatin aggregation in the form of clumps of various shapes and sizes with peripheral localization of chromatin (dots on (d)), dilatation of mitochondria, vacuolization of cytoplasm (dots on (f)); all electron microscopy images are obtained on magnification $\times 8000$ (c-f).

Changes characterized by pronounced polymorphism in the structure of white pulp have been revealed in electron microscopic examination of the spleen of animals after application of xenobiotics. Significant amount of lymphocytes with signs of apoptosis has been detected in white pulp after 7, 15, 30, 45 days of TEPPT and PP application. There is the presence of a condensed, wrinkled cytoplasm, a densified nuclei, which have sinuous contours, chromatin aggregation in the form of clumps of various shapes and sizes, the appearance of clavate protrusions, deep invaginations and constrictions of the nuclear envelope with fragmentation of the nucleus in later stages in such these cells (Fig. 1c-f). Amount of cellular elements of spleen is reduced in 45 days (Table 1).

Table. Influence of the 1/100 LD₅₀ and 1/10 LD₅₀ of TEPPT and PP on the general amount of cellular elements of thymus and spleen in square 10⁴ μm²

Organ	Area of organ	Control	TEPPT		PP	
			1/100 LD ₅₀	1/10 LD ₅₀	1/100 LD ₅₀	1/10 LD ₅₀
Spleen	Mantle zone of follicle	171.1±4.1	152.4±8.4	123.7±10.8*	162.7±7.9	143.6±8.9*
	Marginal zone of follicle	104.6±3.8	89.3±6.9	79.4±9.7*	93.2±6.4	84.2±7.3*
Thymus	Cortical zone of thymus	180.1±3.9	158.4±6.8*	128.3±9.1*	165.9±5.8	148.1±8.5*
	Medullar zone of thymus	137.4±3.7	117.8±7.2	98.6±8.3*	124.7±6.7	108.9±7.6*

note: * - statistically significant differences with the control group (p<0.05)

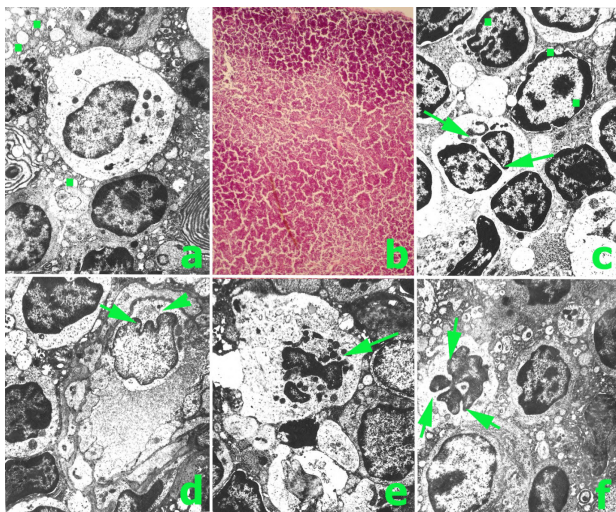


Fig. 2. Electron microscopy of thymus with dense nuclei and the presence of granules or vacuoles filled with amorphous substance in the medullar layer (dots), developed endoplasmaticular reticulum, magnification x8000 (a); Histological structure of thymus after 45 days of treating by solutions of TEPPT in the dose 1/10 LD₅₀, H&E stain, magnification x100 (b); Ultrastructural changes in thymus under influence of xenobiotics with diffuse euchromatin in nuclei, appearance of pronounced invaginations of karyolemma (arrows on (d) and (f)) till fragmentation of nuclei (arrow on (e)), condensed, wrinkled cytoplasm, chromatin aggregation in the form of clumps of various shapes and sizes with peripheral localization (dots on (c)), dilatation of mitochondria, vacuolization of cytoplasm; all electron microscopy images are obtained on magnification x8000 (c-f)

Histological structure of thymus lobules was presented of cortical and medullar substance (Fig. 2b). In the structure of these components, there were very subtle morphological no principal differences. Therefore, when we described the ultrastructure of the cells of the organ under investigation, we considered it possible not to separate the cells of the medulla and cortex separately, especially since the changes observed during the experiment had a similar, unidirectional character.

According to usual structure Gassal's bodies have been detected in the medullar substance as concentric clusters of degenerating stellate thyocytes. Large epithelial have been revealed also as cells with a rounded, weak or medium electron density nucleus and the presence of granules or vacuoles filled with amorphous substance in the medullar layer (Fig. 2a).

Phenomena evidencing both hydropic dystrophy, as well as changes interpreted as signs of apoptosis have been revealed in the epithelial cells. There is significantly increased amount of cells with such changes compared to control group. In particular, apoptosis was indicated by such signs as a sharp increase of the electron-optical density of the cytosol with a decrease in the density of the cytoplasm (cytopiconosis) and shrinkage of the nucleus (karyopiconosis), accompanied by an increase in chromatin condensation in the karyoplasm.

Loosening of the cytosol has been observed in many thymocytes with a decrease in the optical density of the cytoplasm and decrease of the density of the mitochondrial matrix with the enlightment of the organelles and a violation of the ordered arrangement of cristae there, dilatation of the channels of the cytoplasmic reticulum, and decrease in the level of chromatin in the nuclei. The described ultrastructural changes were regarded by us as manifestations of hydropic dystrophy (fig. 2c-f). Amount of cellular elements of thymus is reduced in 45 days of experiment (Table).

Similar changes have been observed in the lymphocytes of the thymus. Thus, in particular, a sharp decrease in the chromatin content has been noted in the nuclei of the cells with clarification of the central part of the nuclei and the condensation of small amounts of heterochromatin near the nuclear membrane. Thus, the obtained results testify about the development of hydropic dystrophy in cellular elements of the thymus on the one hand, and the intensification of apoptosis processes on the other, as influence of TEPPT and PP [10].

So, the revealed structural changes in the spleen of animals indicate the hypoplasia of white pulp, which some authors attribute to the increased incidence of apoptosis and a decrease in the level of cell proliferation in response to the effect of an unfavorable factor [3,6].

Our results clearly show that influence of TEPPT and PP in thymus and spleen is directly involved in thymocyte loss with more active process of involution due to activation of apoptosis and appearance of degenerative changes [16]. They also indicate that spleen is characterized injuring both T-zone and B-zone suppression. It can realize in immunosuppression as evaluation of the immunotoxic potency of agents as part of risk assessment is currently established in vivo with animal models and in vitro with cell lines or primary cells in different organs under influence of xenobiotics [9,14,15].

Ultrastructural changes of thymus and spleen due to the presence of lymphocytes, the immunotoxic effects of xenobiotics or their metabolites on these cell populations may be reflected in the thymus and spleen even more significantly. The two major functional organs of the immune system with specific decreased cellularity, as it could be suggestive of deficits immune responses [1,4].

The induction of 1/10LD₅₀ and 1/100LD₅₀ is characterized severe impact that is apparently explained by the dose, and, hence during investigation was noticed that this dose has statistically significant impact almost on all indicators of cellular morphometry on 45th day.

Conclusions: On the base of obtained results we can conclude that structure of spleen and thymus is susceptible to influence of tryglycidyl ether of polyoxypropylene triol and propylene glycol. Ultrastructural changes in those organs of the immune system are characterized by margination of chromatin in nuclei, appearance of pronounced invaginations of karyolemma till fragmentation of nuclei; condensed, wrinkled cytoplasm, dilatation of mitochondria, vacuolization of cytoplasm. Such changes are manifestation of hydropic dystrophy and apoptosis development with resulting in reducing of cellular density in 45 days more pronounced under TEPPT influence with 1/10 LD₅₀ dose: in mantle zone of spleen follicle from 171.1±4.1 to 123.7±10.8 cells/10⁴ μm², in marginal zone of spleen follicle from 104.6±3.8 to 79.4±9.7, in cortical zone of thymus from 180.1±3.9 to 128.3±9.1, in medullar zone of thymus from 137.4±3.7 to 98.6±8.3.

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SUMMARY

ULTRASTRUCTURAL CHANGES IN THE ORGANS OF THE IMMUNE SYSTEM UNDER THE INFLUENCE OF XENOBIOTICS

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Nowadays scientific achievements in various areas of lives have caused the creation of more and more «foreign body substances» known as xenobiotics. As it is widely accepted that human health is a product of both genetics

and the environment; and premise that also holds true for the immune system with unclear morphogenetic aspect, so we selected the purpose of our work as detection of ultrastructural changes in the spleen and thymus under the influence of tryglycidyl ether of polyoxypropylenetriol (TEPPT) and propylene glycol (PP).

Subacute experiment has been performed on the matured male rat's with administration of 1/10 LD₅₀ and 1/100 LD₅₀ of TEPPT and PP during 7 days, 15 days, 30 days and 45 days. Obtained materials of spleen and thymus have been investigated with ultramicroscopic and histological examination. Detection of cellular density has been performed.

On the base of obtained results we can conclude that structure of spleen and thymus is susceptible to influence of TEPPT and PP. Ultrastructural changes in those organs of the immune system are characterized by margination of chromatin in nuclei, appearance of pronounced invaginations of karyolemma till fragmentation of nuclei; condensed, wrinkled cytoplasm, dilatation of mitochondria, vacuolization of cytoplasm. Such changes are manifestation of hydropic dystrophy and apoptosis development with resulting in reducing of cellular density in 45 days more pronounced under TEPPT influence with 1/10 LD₅₀ dose: in mantle zone of spleen follicle from 171.1±4.1 to 123.7±10.8 cells/10⁴ μm², in marginal zone of spleen follicle from 104.6±3.8 to 79.4±9.7, in cortical zone of thymus from 180.1±3.9 to 128.3±9.1, in medullar zone of thymus from 137.4±3.7 to 98.6±8.3.

Keywords: spleen, thymus, immunotoxicology, morphology, xenobiotics, polyesters, propylene glycol.

РЕЗЮМЕ

УЛЬТРАСТРУКТУРНЫЕ ИЗМЕНЕНИЯ ОРГАНОВ ИММУННОЙ СИСТЕМЫ ПОД ВОЗДЕЙСТВИЕМ КСЕНОБИОТИКОВ

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Целью исследования явилось определение ультраструктурных изменений селезенки и тимуса под воздействием триглицидилового эфира полиоксипропиленetriола и полипропиленгликоля.

При проведении подострого эксперимента изучали ультраструктурные изменения селезенки и тимуса зрелых крыс-самцов после введения 1/10 LD₅₀ и 1/100 LD₅₀ триглицидилового эфира полиоксипропиленetriола (ТЭППТ) и пропиленгликоля (ПП) на протяжении 7, 15, 30 и 45 дней. Полученный материал изучали с помощью электронной и световой микроскопии. Определяли клеточную плотность.

На основании полученных результатов следует заключить, что ткань селезенки и тимуса чувствительна к воздействию ТЭППТ и ПП. Ультраструктурные изменения в органах иммунной системы характеризуются маргинацией хроматина в ядрах, появлением выраженных инвагинаций кариолемы вплоть до фрагментации ядер; конденсацией цитоплазмы, дилатацией митохондрий, вакуолизацией цитоплазмы. Такие изменения соответствуют развитию гидрической дистрофии и апоптоза, что приводит к снижению клеточной плотности спустя 45 дней, более выраженному при воздействии ТЭППТ в дозе 1/10 LD₅₀: в мантийной зоне фолликула селезенки - с 171,1±4,1 до 123,7±10,8 клеток/10⁴μм², в маргинальной зоне фолликула селезенки - с 104,6±3,8 до 79,4±9,7, в кортикальной зоне тимуса - с 180,1±3,9 до 128,3±9,1, в мозговой зоне тимуса - с 137,4±3,7 до 98,6±8,3.

რეზიუმე

იმუნური სისტემის ორგანოების ულტრასტრუქტურული ცვლილებები ქსენობიოტიკების მოქმედების ფონზე

ო. ავილოვა, დ. შიიანი, დ. მარაკუშინი, ვ. ეროხინა,
ვ. გარგინი

ხარკოვის ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

სამუშაოს მიზანს წარმოადგენდა ელენთის და თიმუსის ულტრასტრუქტურული ცვლილებების გამოვლენა პოლიოქსიპროპილენტრიოლის ტრიგლიციდიდული ეთერის (პტტე) და პოლიპროპილენგლიკოლის (პპ) ზმოქმედების ფონზე.

ქვემოწვევ ექსპერიმენტში შესწავლილია ზრდასრული მამრი ვირთაგვების ელენთის და თიმუსის ულტრასტრუქტურული ცვლილებები 1/10 LD₅₀ და 1/100 LD₅₀ პტტე-ს და პპ-ს შეყვანის შემდეგ 7, 15, 30 და 45 დღის განმავლობაში. მიღებული მასალა შეისწავლებოდა ელექტრონული და სინათლის მიკროსკოპით. განისაზღვრებოდა უჯრედული სიმჭიდროვე.

მიღებული შედეგების საფუძველზე დადგინდა, რომ ელენთის და თიმუსის ქსოვილი მგრძობიარეა პტტე-ის და პპ-ის მოქმედების მიმართ. იმუნური სისტემის ორგანოებში განვითარებული ულტრასტრუქტურული ცვლილებები ხასიათდება ქრომატინის მარგინაციით ბირთვებში, კარიოლემის გამოხატული ინვაგინაციების გაჩენით, ბირთვების ფრაგმენტაციამდე კი, ასევე, ციტოპლაზმის კონდენსაციით, მიტოქონდრიების დილატაციით, ციტოპლაზმის ვაკუოლიზაციით. ასეთი ცვლილებები შეესაბამება დისტროფიის და აპოპტოზის განვითარებას, რაც განაპირობებს უჯრედული სიმჭიდროვის შემცირებას 45

დღის შემდეგ, უფრო გამოხატულს პპტეის ზემოქმედების შემდეგ დოზით 1/10 LD₅₀: ელენთის ფოლიკულის მანტიის ზონაში 171,1±4,1-დან 123,7±10,8 უჯრედამდე/10⁴მკმ² ელენთის ფოლი-

კულის მარგინალურ ზონაში - 104,6±3,8-დან 79,4±9,7-მდე, თიმუსის კორტიკულ ზონაში - 180,1±3,9-დან 128,3±9,1-მდე, თიმუსის ტვინოვან ზონაში - 137,4±3,7-დან 98,6±8,3-მდე.

КОРРЕЛЯЦИЯ СТЕПЕНИ МЕХАНИЧЕСКОЙ БОЛЕВОЙ ЧУВСТВИТЕЛЬНОСТИ С КОНЦЕНТРАЦИЕЙ БЕЛКА μ -ОПИОИДНОГО РЕЦЕПТОРА В РАЗЛИЧНЫХ ФАЗАХ ОВАРИАЛЬНО-МЕНСТРУАЛЬНОГО ЦИКЛА

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На сегодняшний день установлено колебание степени выраженности многих физических и психологических симптомов, в том числе головной боли, кровяного давления, вздутия живота, депрессии и тревоги, во время овариально-менструального цикла (ОМЦ) [34,36]. Результаты большого числа исследований, проведенных на животных, а также нескольких работ с участием женщин-добровольцев, показывают влияние половых гормонов на болевую чувствительность и реакцию на анальгетики [1,11,15,24,41]. Вследствие чего, изучение влияния ОМЦ на ноцицептивную реактивность является актуальным для многих направлений клинических исследований, в том числе выявления гормональных модуляторов боли, повышения качества диагностики, а также разработки новых подходов к лечению и профилактике острого и хронического болевого синдрома у женщин.

На основании метаанализа исследований боли был сделан вывод, что в лютеиновой фазе ОМЦ в сравнении с фолликулярной отмечалось усиление болевой чувствительности, индуцированной термическими, механическими и электрическими стимулами [36]. Однако, в более поздних исследованиях получены противоречащие друг другу результаты [7,37]. Противоречивые результаты выявлены также при изучении влияния некоторых отдельных половых гормонов на болевую чувствительность, в том числе при введении гормональных препаратов, в частности имеются данные о повышении механического болевого порога на фоне приема препарата искусственного прогестерона среди 188 здоровых добровольцев [28], аналогично у лабораторных крыс-самок после приема прогестерона отмечалась анальгезия [19], в то же время, в другом исследовании, проведенном на лабораторных мышцах-самках, обнаружено развитие гипералгезии после подкожного введения прогестерона [42]. Различные результаты получены также при изучении влияния пролактина на болевую чувствительность. В результате некоторых исследований [20,33] установлено, что данный гормон не оказывает какого-либо влияния на болевой порог, либо порог болевой чувствительности, в то же время имеются данные

о роли пролактина как негативного модулятора болевой чувствительности [22].

Авторы нескольких работ ставят под сомнение возможность формулировки окончательных выводов на основании некоторых вышеупомянутых исследований исходя из наличия нескольких методологических ограничений в примененных процедурах [7,17]. В нескольких из вышеперечисленных исследований среди участниц не проводился сбор анамнестических данных о регулярности ОМЦ. Во многих исследованиях отсутствовали данные об определении концентрации половых гормонов с целью уточнения фаз ОМЦ [17,18,39]. Кроме того, большинство исследований проведено на небольших группах объектов. Несмотря на то, что привлечение большого количества участниц в исследования ОМЦ сопряжено с определенными трудностями, исследования на небольших выборках не позволяют обобщить результаты, понижают их достоверность, либо приводят к ложным результатам [7].

В формировании острого и хронического болевого синдрома, наряду с ноцицептивной системой, активно участвует эндогенная опиоидная система [43]. Среди структур, принадлежащих к эндогенной опиоидной системе, ключевая роль принадлежит μ -опиоидному рецептору (MOR), активация которого происходит при взаимодействии с эндогенными, либо экзогенными опиатами. В результате активации расположенных на пресинаптических терминалях ноцицептивных нейронов MOR, посредством ингибирования потенциалзависимых кальциевых каналов, происходит уменьшение высвобождения медиатора, что приводит к снижению проводимости нервных импульсов от ноцицепторов в центральную нервную систему. Локализованные также и на постсинаптической терминали MOR обеспечивают понижение возбудимости путем активации G-белок управляемых K-каналов [38]. Результаты многочисленных исследований последних лет указывают на тканеспецифические модулирующие влияния эндогенных агентов, сопутствующих различным патологическим процессам, а также фармакологических веществ на экспрессию гена MOR, и соответственно на изменение концентра-