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INFLUENCE OF THE 30-DAYS CENTRAL DEPRIVATION OF TESTOSTERONE SYNTHESIS ON THE MORPHOLOGICAL AND FUNCTIONAL FEATURES OF RAT TESTICULAR INTERSTITIAL ENDOCRINOCYTES AND SUSTENTOCYTES

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We found out that in the early stages of central deprivation of rat testosterone synthesis cells with ultrastructural signs of functional tension appeared in the population of sustentocytes and interstitial endocrinocytes, which were directed to support testicular secretion function. Central deprivation of testosterone synthesis causes the development of oxidative stress in rat testes, reduces the activity of the arginase pathway of L-arginine metabolism and changes the source of NO production from constitutive isoforms of NO synthase to inducible isoform. Identified metabolic and functional disorders of these cells lead to disorders in spermatogenesis.

Key words: testes, interstitial endocrinocytes, sustentocytes, NO synthase, iNOS, cNOS, L-arginine, superoxide dismutase, NF-kB-COX2, rats.

The work is a fragment of the research project "Experimental morphological study of cryopreserved placenta transplants action, diferelin, ethanol and 1% methacrylic acid on the morphofunctional status in a number of internal organs", state registration No. 0119U102925.

An actual problem of our time is the study of the morphological and functional state of testes' structural components under conditions of a decrease in the male fertility influenced by internal and external factors, which affect the course of spermatogenesis. One of the internal factors affecting male fertility is deficiency or excess of testosterone production.

Ultramicroscopic studies of the testes help to reveal the cooperative effects of sustentocytes and interstitial endocrinocytes when exposed to various factors, which can lead to infertility. Decreased testosterone production can trigger germ cell apoptosis in testes tissues by activation of granzyme-dependent apoptosis [4].

Testosterone deficiency is observed in men with age and is associated with a decrease in its production by interstitial endocrinocytes. One of the regulators of testosterone synthesis is nitric oxide (NO). A high correlation and associative relationship between the level of testosterone and nitric oxide in the blood was established during sexual stimulation [2]. However, this effect depends on the source of NO production. And is true only in the case of NO production from the endothelial isoform of NO synthase [8].

The features of the ultrastructural organization of spermatogenous epithelium and interstitial tissue of testes with its cellular composition during various phases of spermatogenesis under influence of chemical castration by triptoreline are not fully understood. Testosterone is an important biological regulator of testes tissues homeostasis, therefore, from a theoretical and practical point of view, it is necessary to conduct studies of interstitial endocrinocytes and sustentocytes with the determination of nitric oxide production sources and state of above-mentioned cells during various types of spermatogenesis.

The purpose of the study was to clarify the microscopic organization of interstitial endocrinocytes and sustentocytes, to determine the sources of nitric oxide and the intensity of oxidative stress in rat testes during experimental central deprivation of testosterone synthesis with triptoreline.

Materials and methods. We conducted experiments on 10 mature male white rats of the Wistar line. We divided animals into 2 groups: 5 rats made up the control group, which received subcutaneous administration of saline solution during 30 days; 5 rats made up the experimental group, which received subcutaneous administration of diphereline (Triptorelin embonate) at a dose of 0.3 mg / kg during 30 days [4]. Animals were kept under standard vivarium conditions. Experimental animals were removed from experiment in strict accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), as well as the "General Ethical Principles of Animal Experiments" adopted by the first national congress on bioethics (Kyiv, 2001).

After overdosage by ketamine animals were decapitated. Small prepared pieces of testes were fixed in a 2.5% glutaraldehyde solution prepared on phosphate buffer with pH 7.2 – 7.4. Postfixing of the material was carried out with a 1% solution of osmium (IV) oxide, followed by dehydration in propylene oxide and pouring into the mixture of epoxy resins. Ultrathin sections made on an ultramicrorotome were contrasted

with a 1% aqueous solution of uranyl acetate and lead citrate by Reynolds method and studied in an electron microscope. Using standard methods, the material was enclosed in paraffin blocks, from which slices with thickness of 4 μm were made and stained with hematoxylin and eosin. Histological preparations were studied using a light microscope equipped with digital microphotometer Olympus C 3040-ADU and special, adapted for these studies, digital programs (Olympus DP - Soft, license number VJ285302, VT310403, 1AV4U13B26802) and Biorex 3 (serial number 5604).

All biochemical studies were carried out in 10% homogenate of testes tissue using a spectrophotometer Ulab 101. The total activity of NO synthases (NOS) was determined according to the method described in [1]. The activity of constitutive NOS isoforms (cNOS) and inducible isoform (iNOS) were determined according to the procedure described in [11]. The nitrite concentration was determined by the Griss-Ilosvay method [1]. The activity of arginases was determined by the increase in the concentration of L-ornithine after a 20-hour incubation in phosphate buffer medium (pH = 7.0) in the presence of a 24 mM solution of L-arginine [1]. Basic production of superoxide anion radical ($O_2^{\bullet-}$), its production from the mitochondrial electron transport chain (ETC) and microsomal ETC was determined according to the method proposed in the article [7]. The activity of superoxide dismutase (SOD) and catalase was determined according to the guidelines. The concentration of free malondialdehyde (MDA) was determined by the method [7].

Statistical processing of the research results was carried out using the Microsoft Office Excel program and the Real Statistics 2019 extension. The nonparametric Mann-Whitney test was used to determine the statistical significance of differences between groups. The difference was considered statistically significant if $p < 0.05$.

Results of the study and their discussion. On a micropreparation in the seminiferous tubules of rats of the control group, all cellular associations characteristic of spermatogenic epithelium were noticeable: spermatogonia are located on the basal membrane, further from it are located spermatocytes, spermatids and spermatozoa are located in the lumen of the tubules. Their cellular composition indicated various stages of normal spermatogenesis. On the cross section of the testes of rats of the control group, the seminiferous tubules had a rounded shape. Closer to the basal membrane, the nuclei of the Sustentocytes were well visualized. The testicular stroma was represented by loose fibrous connective tissue, in which groups of interstitial endocrinocytes of 3-5 cells in the field of vision, blood vessels and cellular elements were clearly distinguished. The vessels were moderately filled by blood elements (fig. 1).

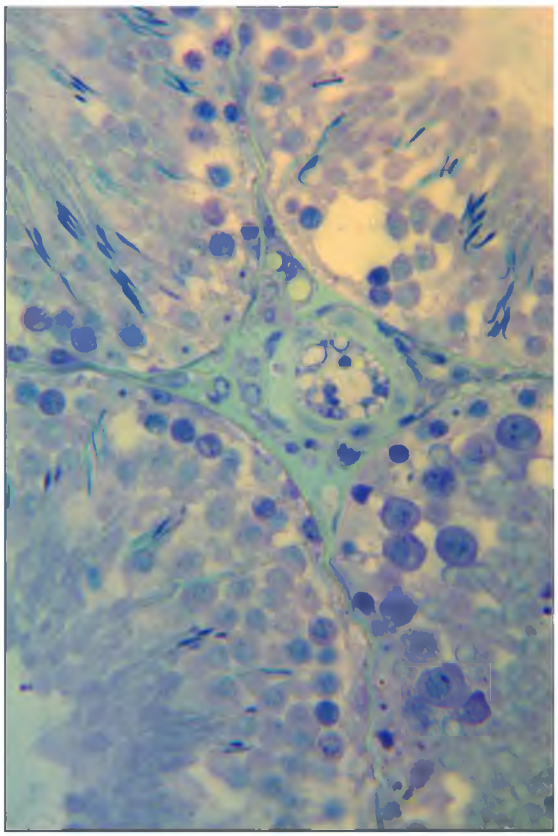

Fig. 1. Semeniformer tubes of experimental mouse. 1 month. Microimage. H&E stain: Lens: 40: Ocular lens:15.

The interstitial endocrinocytes had round-shaped nuclei, located near the blood vessels or peritubularly, in groups or singly. They had rounded nuclei with 1-2 nucleoli. In their cytoplasm was well developed smooth endoplasmic reticulum, which was represented by numerous tubes that branched and were filled with a fine fiber substance, on the membranes of which there were numerous ribosomes. Mitochondria were small, with an osmiophilic matrix and a small number of cristae. A characteristic feature was the presence in the cytoplasm of secretory granules of various sizes and electron densities; they were localized in a well-developed plate apparatus of the Golgi cytoplasmic complex. The cytoplasmic membrane had structure of the elementary membrane.

During examination of sustentocytes, we revealed that they were located on the basal membrane of the convoluted seminiferous tubules. In the basal part of the cells was a large nucleus, which had a homogeneous nucleoplasm; karyolemma had a clear outline. In the cytoplasm of the sustentocyte, it was possible to visualize mitochondria, the shape of which was determined by the cut plane. Mitochondria were characterized by the presence of a matrix with a high electron density, against the background of which vesicles- cristae were well contrasted in the

form of light and round bubbles. The granular endoplasmic reticulum was represented by flattened membrane cisterns whose walls were coated with ribosomes, the elements of the smooth endoplasmic reticulum appeared as membrane vesicles, and numerous lysosomes were also present. Elements of the cytoskeleton were visible in all parts of the cytoplasm of the sustentocytes, with a predominance in the apical fragments, where the heads of maturing spermatids were immersed, fixed with the help of a tubulobulbar complex, and in areas of specialized contacts.

Specialized contacts of the sustentocytes divided the space of seminiferous tubules into two compartments (basal and adluminal parts). In the course of contacts, there appeared zones of ectoplasmic specialization, which performed an isolating function. Inclusions in the cytoplasm of the sustentocytes consisted from glycogen rosettes and, in the basal sections of the cytoplasm, a moderate amount of lipid drops.

In the experimental group of animals (1 month of the experiment), it we observed minor destructive disorders in the ultrastructural organization of the lamellar cytoplasmic Golgi complex of interstitial endocrinocytes (fig. 2).

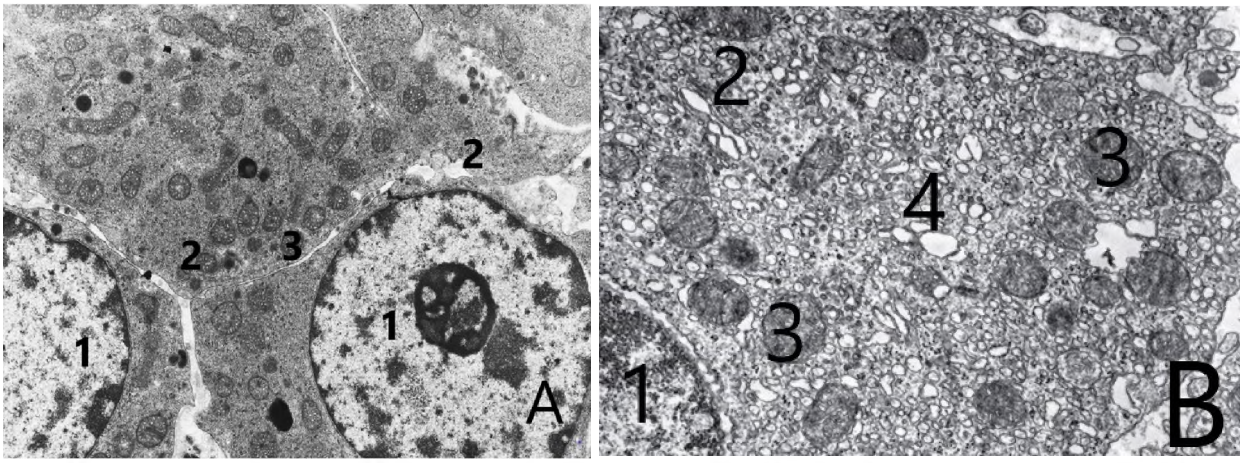

Fig. 2. At electron micrograph of intact (A) and experimental mouse of interstitial endocrinocytes (B). 1 – nucleus of interstitial endocrinocytes, 2 – cytoplasm of interstitial endocrinocytes, 3 – mitochondria, 4 – smooth endoplasmic reticulum . Exp. x 10000.

In some interstitial endocrinocytes, the smooth membranes of the Golgi complex were randomly oriented and surrounded by single large electron-transparent vacuoles, lipid inclusions, and secretory granules. The cytoplasmic membrane of glandulocytes was dissolved, thickened, and had a high electron density. A small number of interstitial endocrinocytes had a fragmented smooth endoplasmic reticulum. The hyaloplasm of glandulocytes was significantly more transparent and contained very few free ribosomes and polysomes, compared with the control group of animals.

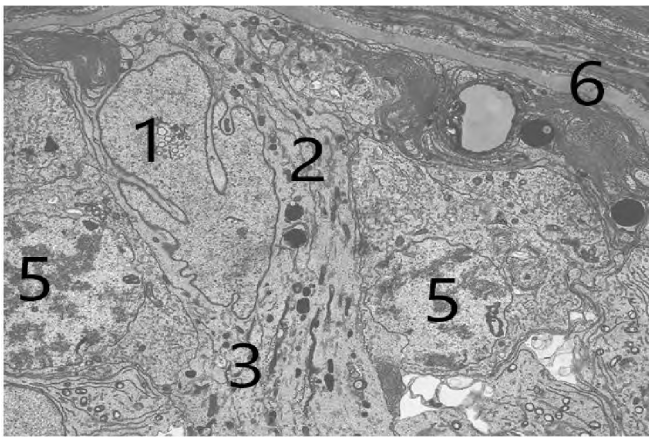

Fig. 3. At electron micrograph experimental mouse sustentocytes. 1 – nucleus sustentocytes, 2 – cytoplasm of sustentocytes, 3 – smooth endoplasmic reticulum, 4 – mitochondria, 5 - nucleus of spermatocytes, 6 – basal membrane. Exp. x 10000.

When studying the ultrastructural organization of sustentocytes from experimental group of rats, the fine structure of which generally corresponded to the control group, we observed appearance of cells with developed adaptive reactions in the cytoplasm, which should be addressed in more detail. Sustentocytes were determined, in the cytoplasm of which we observed hyperplasia of the elements of the smooth endoplasmic reticulum, the morphological equivalent of which were numerous small and expanded round vesicles, localized mainly in the apical sections of cells. The heads of maturing spermatids with the violation of the structures of the tubulo-bulbar complex with primary signs of degeneration were also found in these fragments of the sustentocytes. Quite large phagosomes containing fragments of dead cells turned were observed in the cytoplasm of the sustentocytes. The intercellular contacts between the round spermatids and sustentocytes we re not broken, but the deformation of the inner membranes and vacuolization of mitochondria appeared in the cytoplasm of some spermatocytes, round and maturing spermatids (fig.3).

The number of mitochondria decreased in the cytoplasm of the sustentocyte, the electron density of the mitochondrial matrix also decreased. Ultra-structural signs of slight degradation of the membrane structures of the cytoplasm in the form of concentric electron-dense formations were found in the cytoplasm of vacuolated sustentocytes; protein structures were present either inside the vacuoles or independently located in the cell cytoplasm. The number of lipid drops in the basal cytoplasm of the sustentocytes was increased compared with the control group.

Under conditions of central deprivation of testosterone synthesis in the tissues of the testes, the basic $O_2^{\bullet-}$ production increased by 6.92 times, from mitochondrial ETC $O_2^{\bullet-}$ production increased by 1.99 times, from microsomal ETC by 1.86 times (table 1). SOD activity decreased 3.46 times, catalase activity decreased 2.04 times. At the same time, the concentration of MDA increases by 3.59 timed.

Total NO production from NO synthases did not statistically significantly change (table 2). However, there was a change in the source of NO production, which was manifested by a statistically significant decrease in NO production from constitutive NOS isoforms by 3.73 times. At the same time, there was an increase in iNOS activity by 3.77 times. The activity of arginases was reduced by 7.75 times. The nitrite content in the tissues of the testes did not statistically significantly change.

Table 1

Oxidative stress markers in rat testes during 30-day central testosterone synthesis deprivation (M±m)

Groups	Parameters					
	SOD activity, c.u.	Catalase activity, nkat/g of tissue	Basic $O_2^{\bullet-}$ production, nmol/s per g of tissue	Production of $O_2^{\bullet-}$ from mithochondrial ETC, nmol/s per g of tissue	Production of $O_2^{\bullet-}$ from microsonal ETC, nmol/s per g of tissue	Free MDA, µmol/g of tissue
Control	1.87±0.11	182±17	0.26±0.01	7.84±0.13	9.55±0.19	6.64±1.44
Experimental	0.54±0.20*	89±1*	1.8±0.04*	15.60±0.11*	17.81±0.28*	23.82±0.39*

Note: * - indicates that the difference is statistically significant when compared with control group ($p<0.05$)

Table 2

Nitric oxide cycle function during 30-day cntral testosterone synthesis deprivation (M±m)

Groups	Parameters				
	Total NOS activity, µmol/min per g of protein	iNOS activity, µmol/min per g of protein	cNOS activity, µmol/min per g of protein	Arginase activity, µmol/min per g of protein	NO^{2-} concentration, nmol/L
Control	0.54±0.04	0.13±0.02	0.41±0.03	2.48±0.05	3.83±0.25
Experimental	0.60±0.03	0.49±0.03*	0.11±0.02*	0.32±0.02*	3.83±0.21

Note: * - indicates that the difference is statistically significant when compared with control group ($p<0.05$)

Given the characteristic changes in the ultrastructure of interstitial endocrinocytes and sustentocytes, it can be assumed that the main producers of $O_2^{\bullet-}$ from mitochondrial ETC are interstitial endocrinocytes, and from microsomal ETC - sustentocytes. This statement is supported by following ultrastructural changes: a fragmented smooth endoplasmic reticulum in interstitial endocrinocytes and hyperplasia of the elements of the smooth endoplasmic reticulum in sustentocytes cells with a decrease in the number of mitochondria and reduction in the electron density of the mitochondrial matrix.

Thus, the development of oxidative stress is observed in the tissues of the testes. Oxidative stress can lead to a decrease in testosterone production by interstitial endocrinocytes cells through activation of the NF-kB-COX2 cascade [12]. The involvement of the transcription factor NF-kB in the development of changes in the metabolism of the testes is evidenced by an increase in iNOS activity. Nitric oxide, which was produced by iNOS does not enhance, but inhibits the production of testosterone by interstitial endocrinocytes, since it contributes to the development of oxidative-nitrosative stress [3].

Testosterone has the ability to reduce iNOS activity not only in the testes, but throughout the body, especially in the brain tissue, as shown by Atallah A. et al. [2]. A feature of the testes, in this case, is the presence of a local producer of testosterone - interstitial endocrinocytes, which should compensate for testosterone deficiency. However, based on the results obtained in our research, they are exposed to oxidative stress and are not able to fulfill their hormone-producing function.

Another mechanism underlying the decrease in testosterone production is a decrease in the activity of cNOS, namely the endothelial isoform of NOS. Since the activity of arginases in the testes decreases several times, it is not possible to talk about the feasibility of "arginine steal" from cNOS by these enzymes. A decrease in arginase activity is a negative factor that further aggravates malfunctions in spermatogenesis,

since the end products of the arginase pathway of L-arginine metabolism are polyamines (spermine, spermidine, putrescine), necessary for physiological proliferation and sperm maturation [6].

At the same time, some researchers show that inhibition of arginases by polyphenols has a positive effect on spermatogenesis and testosterone production, eliminating erectile dysfunction [5]. Thus, the importance of arginases in the development of spermatogenesis disorders is ambiguous and requires further study.

Testosterone deficiency as a result of central inhibition of its synthesis can also be the primary cause of oxidative stress, since testosterone has the ability to reduce the formation of reactive oxygen species by mitochondria and reduce the development of stress of the endoplasmic reticulum [9]. An increase in $O_2^{\bullet-}$ production from mitochondrial ETC and microsomal ETC indicates a decrease in the inhibitory effect of testosterone on the production of reactive oxygen species from mitochondria and the development of stress of the endoplasmic reticulum, which is infrastructurally clearly manifested in interstitial endocrinocytes.

Conclusion

Ar the early stages of central deprivation of testosterone synthesis in animals, we found out that cells with ultrastructural signs of functional stress appear in the population of sustentocytes and interstitial endocrinocytes and that reaction is aimed at supporting the secretory function of the testes.

Central deprivation of testosterone synthesis causes the development of oxidative stress in the testes, reduces the activity of the arginase pathway of L-arginine metabolism and changes the source of NO production from constitutive isoforms of NO synthase to inducible isoform.

Identified metabolic and functional disorders of these cells lead to impaired spermatogenesis.

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Реферати

ВПЛИВ 30 ДЕННОЇ ЦЕНТРАЛЬНОЇ ДЕПРИВАЦІЇ СИНТЕЗУ ТЕСТОСТЕРОНА НА МОРФОФУНКЦІОНАЛЬНІ ОСОБЛИВОСТІ ІНТЕРСТИЦІАЛЬНИХ ЕНДОКРИНОЦИТІВ ТА СУСТЕНТОЦИТІВ ЯЄЧКА ЩУРІВ

Стецук Є.В., Костенко В. О., Шепітько В.І., Гольцев А.М.

На ранніх етапах центральної депривації синтезу тестостерону у щурів встановлено, що в популяції сустентоцитів та інтерстиціальних ендокриноцитів

ВЛИЯНИЕ 30 ДНЕВНОЙ ЦЕНТРАЛЬНОЙ ДЕПРИВАЦИИ СИНТЕЗА ТЕСТОСТЕРОНА НА МОРФОФУНКЦИОНАЛЬНЫЕ ОСОБЕННОСТИ ИНТЕРСТИЦИАЛЬНЫХ ЭНДОКРИНОЦИТОВ И СУСТЕНТОЦИТОВ ЯИЧКА КРЫС

Стецук Е.В., Костенко В.А., Шепитько В.И., Гольцев А.Н.

На ранних этапах центральной депривации синтеза тестостерона у крыс установлено, что в популяции сустентоцитив и интерстициальных эндокриноцитов

з'являються клітини з ультраструктурними ознаками функціональної напруги, спрямованих на підтримку секреторної функції яєчка. Центральна депривація синтезу тестостерону викликає розвиток оксидативного стресу в сім'яниках, знижує активність аргіназного шляху метаболізму L-аргініну і змінює джерело продукції NO з конститутійних ізоформ NO-синтази на індуцибельну. Виявлені порушення метаболічної і функціональної активності цих клітин і призводять до порушень сперматогенезу.

Ключові слова: сім'яники, інтерстиціальні ендокриноцити, сустентоцити, NO-синтаза, iNOS, cNOS, L-аргінін, супероксиддисмутаза, NF-kB-COX2, щури.

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появляются клетки с ультраструктурными признакам функционального напряжения, направленными на поддержку секреторной функции яичка. Центральная депривация синтеза тестостерона вызывает развитие оксидативного стресса в семенниках, снижает активность аргиназного пути метаболизма L-аргинина и меняет источник продукции NO с конститутивных изоформ NO-синтазы на индуцибельную. Выявленные нарушения метаболической и функциональной активности этих клеток и приводят к нарушениям сперматогенеза.

Ключевые слова: семенники, интерстициальные эндокриноциты, сустентоциты, NO-синтаза, iNOS, cNOS, L-аргинин, супероксиддисмутаза, NF-kB-COX2, крысы.

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ВПЛИВ ЛІОФІЛІЗОВАНОГО ЕКСТРАКТУ З ТРАВИ ХАМЕРІЮ ВУЗЬКОЛИСТОГО НА ГІСТОЛОГІЧНИЙ СТАН ПЕЧІНКИ ЩУРІВ ЗА УМОВ ГОСТРОГО ТОКСИЧНОГО УРАЖЕННЯ ТЕТРАХЛОРМЕТАНОМ

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У дослідах на білих щурах досліджена гістологічна структура печінки за умов гострого токсичного ураження після введення екстракту хамерію та препарату порівняння «Силібініну». Виявлено, що досліджуваний екстракт має виразний захисний вплив на мікроскопічну будову печінки. Одержані морфологічні дані засвідчили, що екстракт хамерію суттєво зменшує пошкоджуючу дію тетрахлорметану та сприяє активному відновленню паренхіми печінки, має кращий позитивний ефект порівняно з препаратом порівняння «Силібінін». Позитивний вплив досліджуваного засобу проявляється активацією регенераторних процесів, що покращує структурну організацію печінки тварин після гострого токсичного ураження тетрахлорметаном.

Ключові слова: гістологічне дослідження, печінка, експериментальний токсичний гепатит, тетрахлорметан, ліофілізований екстракт трави хамерію.

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Печінка – один із провідних органів регуляції вуглеводного та ліпідного обміну, депо глікогену, місце синтезу ліпопротеїнів дуже низької щільності. Близько 20 млн. хімічних реакцій щохвилини відбувається в цьому органі [3]. Порушення обміну речовин обов'язково пов'язані зі змінами структури і функцій печінки, тому пошук та дослідження засобів з гепатопротекторною активністю є важливим завданням сучасної експериментальної та клінічної медицини [5]. Сьогодні одним із джерел одержання препаратів з гепатопоротекторною дією є лікарські рослини. Вони мають ряд переваг перед синтетичними, тому що порівняно легко переносяться організмом, не викликають істотних побічних ефектів навіть при тривалому їх застосуванні. Крім того, лікування рослинними засобами є більш доступним, що має важливе значення при хронічних захворюваннях.

Хамерій вузьколистий (Chamerion angustifolium L.) – рослина роду Іван-чай (Chamerion), здавна використовується у народній медицині для лікування мігрені, головного болю, безсоння, анемії, виразкової хвороби шлунка та дванадцятипалої кишки, гастриту, коліту, як протипухлинний і жовчогінний засіб; зовнішньо – для лікування та швидшого загоювання ран та опіків [7]. З огляду на те, що ліофілізований екстракт з трави хамерію (ЛЕТХ) містить загальновідомі за антиоксидантними властивостями фенольні сполуки (флавоноїди, гідроксикоричні кислоти, дубильні речовини) [9], доцільним було дослідити гепатопротекторну активність даного засобу.

Метою роботи було вивчити коригуючий вплив ЛЕТХ на мікроскопічну будову паренхіми печінки та порівняти його ефективність із дією референс-препарату «Силібініну» за умов експериментального токсичного ураження печінки.