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MORPHOLOGICAL CHANGES OF THE PROSTATE GLAND IN EXPERIMENTALLY SIMULATED PROSTATIC HYPERPLASIA AGAINST THE BACKGROUND OF ETHANOL INTOXICATION

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The scientific work is devoted to the study of the peculiarities of the prostate gland morphological changes in simulated benign hyperplasia under the influence of ethanol. The study was conducted on adult white male laboratory rats, weighing 190–250 g, divided into 2 groups. As a result of the study, it was established that during the toxic effect of ethanol on the 28th day of the experiment, venous stasis, destruction and spasm of the arterial bed, reorganization of acini, excretory ducts and components of connective tissue, growth of collagen fibers and periacinar, periductal and perivascular connective tissue fibrosis were present in prostate tissue under conditions of simulated hyperplasia. Lymphocytic infiltration was revealed, the hypertrophied secretory portions were lined mainly with columnar epithelial cells, the lumen was filled with large oxyphilic prostatic concretions. Excretory ducts were characterized by the expansion of lumens with the accumulation of secretions, atrophy of the epithelial layer, edema, and histoleukocyte infiltration. So, under the conditions of simulated alcohol intoxication, destructive and proliferative changes of the secretory departments, excretory ducts, remodeling of the connective tissue components of the prostate gland, which occur against the background of vascular disorders, were established.

Key words: benign prostatic hypertrophy, ethanol, morphology.

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МОРФОЛОГІЧНІ ЗМІНИ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ ПРИ ЕКСПЕРИМЕНТАЛЬНО ЗМОДЕЛЬОВАНІЙ ГІПЕРПЛАЗІЇ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ НА ФОНІ ЕТАНОЛОВОЇ ІНТОКСИКАЦІЇ

Наукова робота присвячена вивченню особливостей морфологічних змін передміхурової залози при змодельованій доброякісній її гіперплазії за дії етанолу. Проводилось дослідження на статевозрілих лабораторних щурах-самцях, масою 190–250 г розділених на 2 групи. В результаті дослідження встановлено, що в процесі токсичного впливу етанолу на 28 добу експерименту у тканині передміхурової залози за умов змодельованій гіперплазії наявні венозний застій, деструкція і спазм артеріального русла, реорганізація ацинусів, вивідних проток та компонентів сполучної тканини, розростання колагенових волокон та фіброзування периацінарної, перидуктальної та периваскулярної сполучної тканини. Виявляється лімфоцитарна інфільтрація, гіпертрофовані секреторні відділи вистелені переважно призматичної форми епітеліальними клітинами, просвіт заповнений великими оксифільними простатичними тільцями. Для вивідних проток характерне розширення просвітів з накопиченням секрету, атрофія епітеліального пласту, набряк та гістолойкоцитарна інфільтрація. Отже, за умов змодельованої алкогольної інтоксикації встановлено деструктивні та проліферативні зміни секреторних відділів, вивідних проток, ремодельовання сполучнотканинних компонентів передміхурової залози, які відбуваються на фоні судинних розладів.

Ключові слова: доброякісна гіпертрофія передміхурової залози, етанол, морфологія.

The study is a fragment of the research project "Pathogenetic features of systemic and organ disorders due to the affection of extraordinary factors on the body", state registration No 0121U100071.

One of the most frequent diseases of the genitourinary system in older men is benign prostatic hyperplasia (BPH), this applies not only to Ukraine, but also to the whole world, in addition, in recent years this disease has been the focus of attention of both urologists and other specialists seek the alternatives that may solve this problem. There was an opinion that violations of urination and erectile function were most often encountered in old age, but today this problem is also observed in middle-aged men, because their reproductive system continues to function differently from the female body, the result of which is a large number of prostate diseases after the age of 45–50 years [11]. The problem of global population aging and related health problems are attracting more and more attention. This is evidenced by sources of information that provide solid arguments and indicate the medical and social relevance of this pathology [6]. In recent years, many scientific studies have been published about the dynamics of the structural organization of the prostate gland and the study of the morphological structure of the organ, which is due to the rapid growth of prostate diseases in all countries of the world. According to the literature, BPH is detected during histological examination in about 20 % of men aged 40–50 years, 50 % at the age of 51–60 years, and 90 % in 80 years old men and older. The age factor is the leading factor in the occurrence of many urological diseases, and there is a direct relationship between the age of the patient and the frequency of prostate gland (PG) diseases, but according to new studies, infectious and inflammatory factors also play an important role in the etiology of BPH [4, 13]. In addition to the widespread prevalence of this problem, it also has a wide negative impact on the entire body, on all organs and systems, and the vascular bed. Due to its toxic effect, ethanol affects the resistive link of the hemomicrocirculatory bed, penetrates it, causing oxidative stress with subsequent

disruption of the work of organs and systems, disturbances in the work of the central nervous system, increases the frequency of infectious diseases, cardiovascular diseases, and according to new scientific studies, increases as well as the prevalence of diseases of the oral cavity mucosa [2, 10]. In recent years, the number of men who systematically and excessively drink alcohol, as well as having concomitant problems with the development of BPH, has increased. The course of benign hyperplasia of the prostate gland in conditions of chronic ethanol intoxication is also the cause of violations of spermatogenesis and testosterone biosynthesis, because it is due to a violation of the testicular androgens that the sexual function of men suffers [3, 5]. Along with this, dystrophic changes occur in the cells of the gland, microcirculation is disturbed, the possibilities of reparation decrease, and lower urinary tract symptoms (LUTS) manifest in parallel.

Therefore, the development of new approaches to the study and diagnosis of morphological changes in benign prostatic hyperplasia under the influence of ethanol remains relevant.

The purpose of the study was to investigate the structural and functional changes in the prostate gland under the influence of ethanol in the experiment.

Materials and methods. To study the course of BPH under ethanol exposure, an experimental study was conducted on 55 adult white male Wistar rats, weighing from 190 to 250 g inclusive, were kept in the vivarium of the Central Research Laboratory of the Ivan Horbachevsky Ternopil National Medical University. Laboratory animals were divided into 2 groups: group I (control group) included 20 intact rats, which were injected with distilled water orally for 28 days and examined for normal ultra- and histostructure of the prostate parenchyma; in animals of the II group (35 animals), the development of BPH was simulated with the help of subcutaneous administration of ampoule 5 % testosterone at a dose of 0.1 mg/kg once a day and the toxic effect of a 40 % ethanol solution at the rate of 2ml/100g of body weight internally once a day lasting 28 days. A biopsy of the prostate gland, which was taken from all studied groups of animals, was subjected to histological examination. After the experiment, microsections were made by pre-fixing the PG tissues in a 10 % neutral formalin solution, and after conventional processing and embedding in paraffin blocks, histological sections with a thickness of 5–6 μm were made and stained with hematoxylin and eosin. Histological slides were studied using a MICROMed SEO SCAN light microscope and photo-documented using a Vision CCD Camera with a system of image output from histological slides.

Results of the study and their discussion. The prostate gland capsule is formed by a thin layer of connective tissue and contains smooth myocytes in it. Trabeculae pass from the capsule inside the organ and divide it into lobules, which are formed by the terminal secretory portions (acini), or glandules. Acini are clearly demarcated by layers of loose connective tissue with numerous smooth myocytes and form a supportive and contractile frame of the organ, contain vessels, nerves and interlobular excretory ducts. The terminal secretory portions are lined with simple columnar or cuboidal epithelium, as well as excretory ducts, the epithelium of which is formed by cuboidal basophilic epitheliocytes. A homogeneous, amorphous prostatic juice is observed in the lumen of the acini.

In the middle of the prostate gland is the prostatic part of the urethra, which is lined with a stratified transitional epithelium. Tubular-alveolar glands of the mucous type of the prostate gland are arranged in three groups, formed by terminal secretory portions or acini and excretory ducts. The first group of small glands is located in the form of a ring around the urethra in the mucosal tunic. Intermediate (submucosal) mucous glands are located in the connective tissue of submucosa of the urethra. The peripheral group of the main glands is the most numerous, the most branched and located in the peripheral area of the prostate gland.

Pathomorphological studies of the prostate gland of experimental animals on the 7th day under the influence of ethanol established a moderate swelling of the stroma of the organ and an increase in cellular elements, mainly of the fibrocytic series. Interlobular stromal connective tissue also contained diffusely located leukocytes. Blood filling of veins and venules, deformation, narrowing of lumens of arteries, arterioles and hemocapillaries, destruction of their walls were characteristic of the vessels of the organ (Fig. 1).

In the secretory portions of the gland, there was an increase in the lumen, which was filled with oxyphilic prostatic secretion. Epitheliocytes of the acini were characterized by an increase in their height, they acquired a highly prismatic shape, with manifestations of hypersecretion.

On the 14th day of experimental exposure to ethanol on the prostate gland of rats, an increase in destructive changes was observed. Narrowing of lumens of arteries, violation of the circular direction of smooth myocytes of the middle tunic of vessels were noted. Veins were characterized by blood filling, stasis, thrombus formation, and perivascular edema. Endotheliocytes of hemocapillaries were swollen, their pyknotic nuclei protruded into the vessel lumen. The stromal connective tissue was swollen, thickened bundles of collagen fibers were found, and histoleukocyte infiltration was present. The narrowing or expansion of the lumen of the acini was revealed, mainly due to the violation of secretion outflow, and their deformation was determined. The condensed epithelium of the secretory portions had a tortuous relief and formed two or three rows of basophilic cells. There were signs of karyopyknosis, compaction and destruction of epitheliocytes, their detachment into the lumen of the secretory portions (Fig. 2).

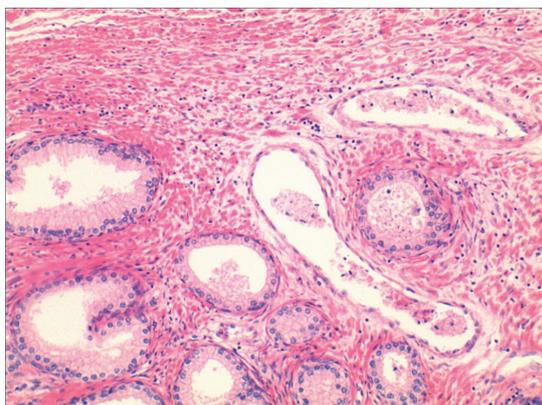


Fig. 1. Morphological changes of the prostate gland of the rat on the 7th day of the experiment. Secretory portions of the gland, infiltration of the stroma and perivascular space of the artery and vein by lymphocytes, destruction of the vessel wall. Staining with hematoxylin and eosin $\times 100$.

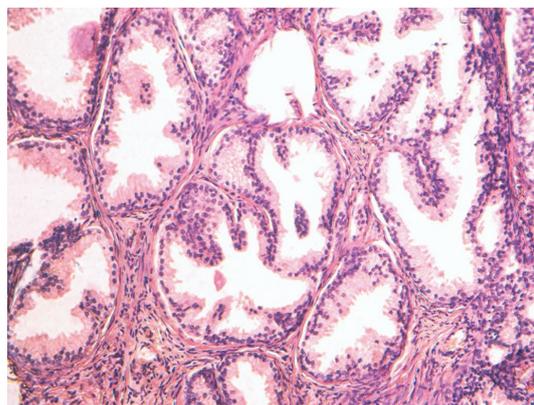


Fig. 2. Morphological changes of the prostate gland on the 14th day of ethanol intoxication. Infiltration and edema of connective tissue trabeculae. Layer-by-layer arrangement and desquamation of mucous epitheliocytes into the lumen of the secretory portion. Staining with hematoxylin and eosin $\times 100$.

Microscopic study of the course of benign hyperplasia of the prostate gland on the 21st day of alcoholization in rats revealed the progression of alterative changes. The swelling of the amorphous component of the intercellular substance of the stromal connective tissue was preserved; thickened, oxyphilic collagen fibers and smooth myocytes were found. Stromal-vascular relations in the organ during this period under the conditions of alcohol influence were disturbed. Arteries and arterioles were characterized by a narrowing of lumens, lightening and swelling of smooth myocytes, their nuclei were pyknotically altered, and their circular orientation in the composition of the media was lost. The lumens of the veins were dilated, filled with blood, with phenomena of stasis, perivascular edema and infiltration of the adventitia were observed. Most hemocapillaries were blood-filled, with a thin wall and pyknotically altered, hyperchromic nuclei.

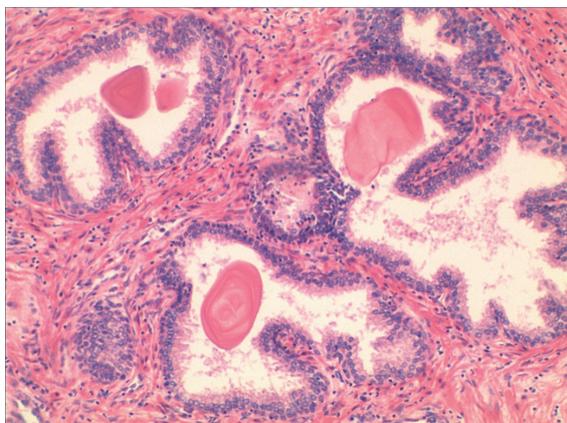


Fig. 3. Morphological changes of the prostate gland on the 21st day of ethanol intoxication. Histoleukocyte infiltration of the connective tissue stroma. Destructively changed epitheliocytes, prostatic concretions in the lumen of the secretory portions. Staining with hematoxylin and eosin $\times 100$.

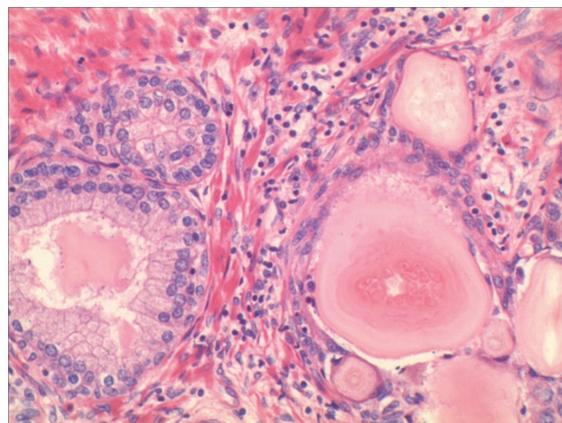


Fig. 4. Morphological changes of the prostate gland of rats on the 28th day under the influence of ethanol. Fibrosis of smooth muscle fibers, histoleukocyte infiltration of stromal trabeculae. Destructive and atrophic changes of the glandular epithelium. Staining with hematoxylin and eosin $\times 200$.

Signs of atrophy and destruction were observed in the secretory epithelium of the acini. Low-columnar or cuboidal epitheliocytes in their composition were densely packed, intensely basophilic and contained pyknotically altered nuclei, which indicated atrophic changes. Destructively changed secretory cells were located in several layers, sometimes exfoliated into the lumen of the acinus. In some hypertrophied glands, desquamated epithelial cells and prostatic concretions were determined in the lumens (Fig. 3).

On the 28th day of ethanol exposure to the prostate gland of experimental animals, the most significant pathomorphological changes were noted. Remodeling of vessel walls with venous stasis and destruction and spasm of the arterial bed were combined with reorganization of acini, excretory ducts, and connective tissue components. In this term, the fibrosis of smooth myocytes and the growth of collagen fibers in the composition of peri-acinar, periductal and perivascular connective tissue were determined (Fig. 4).

Connective tissue trabeculae were represented by thick bundles of collagen fibers interwoven with brightly oxyphilic, numerous smooth myocytes, lymphocytic infiltration was revealed. Irregularly shaped hypertrophied secretory portions were lined mainly with columnar epithelial cells. Lightly oxyphilic

secretory cells of part of the acini formed a multi-layered arrangement of cells. Also, in the composition of the lobule, there were significantly destructively changed secretory portions, the epithelial cells of which acquired a cuboidal and more often squamous shape, and the lumen was filled with large oxyphilic prostatic concretions (Fig. 4). Excretory ducts were characterized by the expansion of lumens with accumulation of secretions, atrophy of the epithelial layer, edema, and histoleukocyte infiltration.

During the morphological study of the dynamics of benign prostatic hyperplasia under conditions of chronic alcohol intoxication on the 7th day of the experiment, alterative changes were established in almost all structures of the prostate gland with their progression up to the 28th day of the experiment. From the results of our research that were compared with the information from the literature, it should be noted that the most significant changes were observed in small-caliber vessels. Veins and venules were blood-filled, there were deformation and destruction of their walls, an uneven increase in the thickness of the intima, media, and adventitia, narrowing of the lumens of arteries, arterioles, and hemocapillaries, which led to dysfunction of vascular structures and severe vascular disorders [5, 1, 14]. Perivascular edema of the stroma, cells of altered and damaged endotheliocytes, myocytes, stasis phenomena, thrombus formation were observed, which indicated hypoxia and violation of structural cellular homeostasis in the organ. Analyzing the structure of the prostate gland in benign hyperplasia under conditions of ethanol intoxication, we found that the microscopic changes were local. A moderate swelling of the stroma of the organ was established, the connective tissue contained diffusely located leukocytes, intercellular contacts and the connection with the basement membrane were partially broken, the nuclei of the endotheliocytes were changed and deformed. According to the researchers, destructive changes were observed both in the main epitheliocytes and the parenchymal cells of the prostate gland lobules [4, 6].

The results of our research made it possible to identify morphofunctional changes in the prostate gland under conditions of ethanol intoxication, which have both theoretical and practical significance for the invention of optimal correction methods for this pathology.

Conclusions

1. Thus, the obtained data confirm the direct, negative effect of ethanol on the parenchyma of the prostate gland with simulated benign prostatic hyperplasia.

2. The results of morphological studies established significant destructive and proliferative changes in secretory portions, excretory ducts, remodeling of connective tissue components of the organ, which occurred against the background of vascular disorders, the degree of manifestation of which increased depending on the duration of the experiment.

3. The obtained results complement the data on morphological changes in benign prostatic hyperplasia in the process of ethanol intoxication. Further study of these histological changes can help avoid the development of various complications and find effective methods of correcting the disorders that have occurred in the gland tissue.

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EVALUATION OF ANTINOCICEPTIVE AND ANTIEXUDATIVE EFFECTS OF A COMPLEX HERBAL PREPARATION IN THE THERAPY OF SOMATIC PAIN AND INFLAMMATION OF DIFFERENT ORIGIN

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Experimental studies of the antinociceptive effect of the complex herbal preparation on models of somatic pain induced by thermal and chemical stimuli were performed, and the antiexudative impact of the drug was established on models of inflammation of various genesis. The experimental sample of the herbal preparation is presented in the form of an ointment for transdermal administration and contains a complex of plant extracts: *Juglans nigra L.*, *Acorus calamus L.*, *Styphnolobium japonicum L.* and *Zingiber officinale L.* The study's results indicate the effectiveness of the drug in treating somatic pain with skin damage and in deep somatic manifestations of pain reactions. The activity of the herbal preparation was not inferior to that of the comparison drug. In the trypsin and zymosan models of edema, the complex herbal preparation has pronounced anti-inflammatory activity when administered transdermally. It suppresses cyclooxygenase and lipoxygenase activity, making it a promising object for further pharmacological study and introduction into medical practice as an alternative means of treating somatic pain and inflammatory processes.

Key words: herbal preparation, antinociceptive and antiexudative action, inflammation, somatic pain.

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ОЦІНКА АНТИНОЦИЦЕПТИВНОЇ ТА АНТИЕКСУДАТИВНОЇ ДІЇ КОМПЛЕКСНОГО ФІТОПРЕПАРАТУ В ТЕРАПІЇ СОМАТИЧНОГО БОЛЮ ТА ЗАПАЛЕННЯ РІЗНОГО ГЕНЕЗУ

Проведено експериментальні дослідження антиноцицептивної дії комплексного фітопрепарату на моделях соматичного болю індукованого термічним і хімічним подразниками та встановлення антиексудативної дії препарату на моделях запалення різного генезу. Дослідний зразок фітопрепарату представлений у вигляді мазі для трансдермального введення та містить комплекс рослинних екстрактів: *Juglans nigra L.*, *Acorus calamus L.*, *Styphnolobium japonicum L.* та *Zingiber officinale L.* Результати дослідження свідчать про ефективність засобу при терапії соматичного болю з пошкодженням шкірних покривів та при глибоких соматичних проявах больових реакцій. Активність фітозасобу не поступалась дії препарату порівняння. На трипсиновій та зимозановій моделях набряку комплексний фітопрепарат при трансдермальному введенні має виражену протизапальну активність, пригнічуючи активність циклооксигенази та ліпооксигенази, що робить його перспективним об'єктом для подальшого фармакологічного вивчення та впровадження в медичну практику як альтернативного засобу терапії соматичного болю та запальних процесів.

Ключові слова: фітопрепарат, антиноцицептивна та антиексудативна дія, запалення, соматичний біль.

The study is a fragment of the research project "Pharmacological correction of simulated pathological conditions by using developed medicines" state registration No. 0122U200545.

Pain and inflammation are one of the most common reactions of a living organism. They often lead to severe suffering and disability and, as a result, to decreased quality of life and sometimes to deaths among patients. Therefore, the problem of treating pain and inflammation is one of the most important tasks in medicine today.