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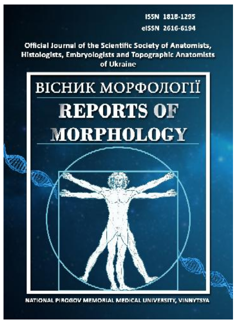

Electron microscopic changes in interstitial endocrinocytes of rats testicles during administration of triptorellin for 365 days

Stetsuk Ye. V., Shepitko V. I., Boruta N. V., Vilkhova O. V., Skotarenko T. A., Rud M. V.

Poltava State Medical University, Poltava, Ukraine

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CORRESPONDING AUTHOR

e-mail: stetsuk78@gmail.com

Stetsuk Y. V.

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Data are available upon reasonable request to corresponding author.

Triptorelin is a gonadotropin-releasing hormone agonist that is a potent inhibitor of testosterone (in men) and estrogen (in women) synthesis and is used to treat advanced prostate cancer. Studies of the mechanisms of regulation and synthesis of testosterone formation in testicular interstitial cells demonstrate multiple endogenous targets that can increase testosterone biosynthesis, which may moderate the effects of testosterone depletion. Triptorelin, a synthetic analog of the neurohormone gonadoliberin, suppresses the expression of the GnRH receptor in the pituitary gland, but does not change the functioning of the pituitary-testicular complex. The purpose of the work is to study the electron microscopic changes in the interstitial endocrinocytes of the testes of rats after the administration of triptorelin for 365 days.The experiment was conducted on 35 sexually mature male white rats. The rats were divided into 2 groups: the control group (I) was injected with a physiological solution, the II group with central deprivation of the synthesis of luteinizing hormone was injected subcutaneously with triptorelin at a dose of 0.3 mg of the active substance per kg of the rat's body weight. The study of the interstitial space in the testicles of white rats showed that long-term administration of triptorelin causes hormonal dysregulation of the hypothalamus-pituitary-testis system, which leads to quantitative and qualitative changes in the endocrine cells of the interstitial space of the testis, which is confirmed by electron microscopic changes in subcellular structures. The maximum effect of triptorelin is determined from the 180th day of observation, which is characterized by an increase in degenerative changes in endocrinocytes, and the detection of Reinke crystals in the cytoplasm of interstitial endocrinocytes from the 270th day of observation.

Keywords: *testes, electron microscopy, rats, interstitial endocrinocytes, luteinizing hormone, triptorelin.*

Introduction

As is known [1, 2, 7, 8], interstitial endocrinocytes maintain a high level of androgen (testosterone or androstenedione), necessary for the differentiation of male genital organs and masculinization of the brain. Androgen production declines with the loss of these cells, reaching its lowest point in the postpartum period. Testosterone levels then gradually increase to high levels with the development of testicular interstitial endocrinocytes from stem cells. In adults, luteinizing hormone (LH), binding to LH receptors of interstitial endocrinocytes, stimulates the production of cAMP, increasing the rate of cholesterol translocation into mitochondria. LH is a gonadotropic peptide hormone of the anterior lobe of the pituitary gland, which stimulates the secretion of sex hormones by the pituitary gland, both in women and in men [4, 6, 13]. In its turn, LH is the central regulator that controls the production of the male sex hormone - testosterone, through the "pituitary - testis" system with the activation of interstitial endocrinocytes to produce testosterone, which in turn stimulates the growth and development of testicular cells and tissues. The increase in testosterone concentration under the influence of LH is due to LH-stimulated proliferation of interstitial endocrinocytes [12]. In conditions of deficiency or complete absence of LH caused by the administration of chemotherapy drugs in oncological pathologies, the death of cells of the seminiferous tubules occurs due to the activation of apoptosis and stress of the endoplasmic reticulum of cells of the spermatogenic series and supporting sustentocytes [15, 18].

Triptorelin, a synthetic analogue of the neurohormone gonadoliberin (gonadotropin-releasing hormone, GnRH) [7, 11], suppresses the expression of the GnRH receptor in the pituitary gland, but did not change the functioning of the pituitary-testicular complex. Physical changes during puberty require the concerted efforts of many organs; these changes are initiated by activation of the hypothalamic-pituitary-gonadal axis. The first hormonal change during puberty is the pulsatile release of GnRH, caused by disinhibition of the hypothalamic-pituitary-gonadal axis [8, 16]. Although the cause of this disinhibition is largely unknown, the subsequent release of GnRH then stimulates pulsatile LH release.

The purpose of the work is to study the electron microscopic changes in the interstitial endocrinocytes of the testes of rats after the administration of triptorelin for 365 days.

Materials and methods

The study was conducted on 35 sexually mature white male rats. Animals were randomly divided into 2 groups: control (10 animals) and experimental (25 animals). Rats from the control group received injection of physiological saline. Experiment lasted 365 days. The animals of the experimental group were injected with a solution of triptorelin acetate at the rate of 0.3 mg of the active substance per kg of animal weight to simulate central deprivation of luteinizing hormone synthesis [5]. Animals were removed from the experiment on the 30th, 90th, 180th, 270th, and 365th days by overdose with ether anesthesia. Animals were kept in standard vivarium conditions of the Poltava State Medical University.

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

Experimental animals were sacrificed in strict compliance 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 with the "General Ethical Principles of Animal Experiments" adopted by the First National Congress on Bioethics (Kyiv, 2001). The research was approved and confirmed by the bioethics commission of the Poltava State Medical University (protocol № 195 - 06.24.2021).

For electron microscopic studies [3], fragments of the organ were fixed in a 2.5% solution of glutaraldehyde, fixed in a 1% solution of osmium tetroxide in a phosphate buffer (pH 7.2-7.4), dehydrated in alcohol and propylene oxide, and poured into a mixture of epoxy resins with araldite. Ultrathin sections were prepared on a ZKB-3 ultramicrotome (Sweden) and grids were made. Sections were contrasted first in a 1 % solution of uranyl acetate in methanol, and then with lead citrate according to Reynolds. The preparations were studied on an electron microscope PEM-125 K (serial number 38-76, TU 25-07-871-70), accelerating voltage 50-75 KW.

Results

One of the features of the endocrinocyte population of the control group of animals was the variety of cell shapes from round, oval to polygonal; in a small amount, there were also cells of a processive and spindle-shaped form. The round cells had a diameter of 14-18 μm. The first three cell forms were characterized by medium and large nuclei and well-developed cytoplasm. In the nuclei, euchromatin is distributed evenly over the entire area, the content of parietal heterochromatin varies. The described morphological characteristics are characteristic of mature, functionally active cells. The analysis of the distribution by groups of cells with different sizes of nuclei showed that in the population of testicular endocrinocytes cells with average sizes of nuclei predominate, there are more than 60% of them. The differentiated cells had a moderately developed smooth endoplasmic reticulum, which often formed large vacuolar expansions. Mitochondria are numerous, the mitochondrial matrix is quite dense, and tubular and mixed cristae are not always visible in it. On the surface of individual cells, there are protrusions of the cytolemma of various shapes. Contacts of cell processes with blood and lymphatic capillaries are often found. In the areas of contact between cells and capillaries in the surface layer of endocrinocyte cytoplasm, there were many exocytotic vesicles. Lipid droplets were large in size, but occurred rarely and not in every cell. The content of lysosomes in the cytoplasm of endocrinocytes is low. The cytoplasmic membrane corresponded structurally to the elementary membrane. Cells are interconnected by desmosomes and gap junctions.

When studying electrograms of an experimental group of animals on the 30th day of observation, we established that interstitial endocrinocytes were located near blood vessels or peritubularly, in groups or singly. They had rounded cores with 1-2 nucleoli. A well-developed smooth endoplasmic reticulum was found in the cytoplasm, which was represented by numerous branching tubules filled with a thin fibrous substance, on the membranes of which numerous ribosomes were present (Fig. 1).

Mitochondria of medium size, with an osmiophilic matrix and a small number of crystals. A characteristic feature was the presence in the cytoplasm of secretory granules of different sizes and electron density, localized in the well-developed lamellar apparatus of the cytoplasmic Golgi complex. Their characteristic feature is the presence of lipid inclusions and small, electron-dense hormonal granules in the cytoplasm. The latter are observed near the well-developed Golgi complex or in peripheral areas of the cytoplasm near the hemocapillary.

The presence of numerous mitochondria, the cristae of which are immersed in a matrix of moderate electron density, is characteristic of the cells of this observation group. The large volume of the cell cytoplasm that belongs to the mitochondria is connected with the fact that the synthesis of steroid hormones started on the endoplasmic reticulum is still being completed in these organelles. A typical picture for

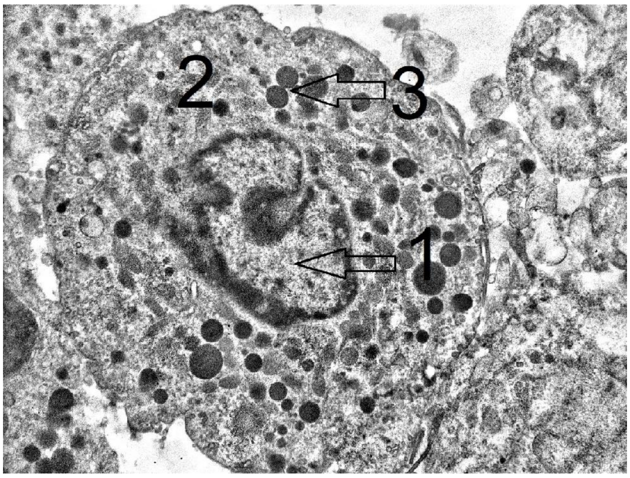

Fig. 1. Endocrinocyte of the stroma of the testis on the 30th day of observation. 1 - endocrinocyte nucleus, 2 - endocrinocyte cytoplasm, 3 - inclusions. x9 000.

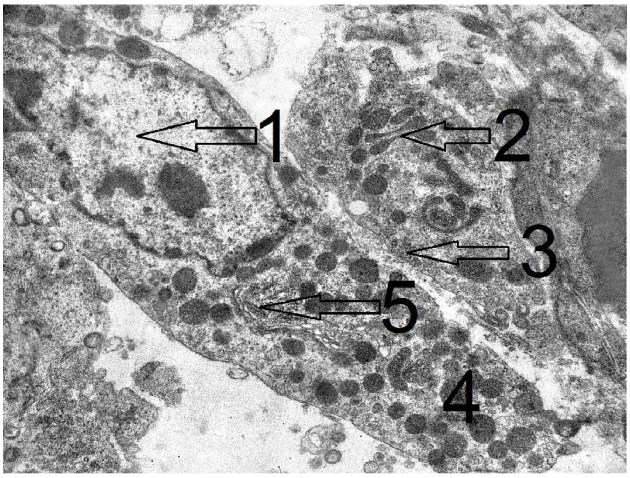

Fig. 2. Endocrinocyte of the stroma of the testis on the 90th day of observation. 1 - endocrinocyte nucleus, 2 - Golgi complex, 3 - mitochondria, 4 - inclusion, 5 - endoplasmic reticulum. x9 000.

cells is the close contact of mitochondria with elements of the endoplasmic smooth reticulum.

In the experimental group of animals, on the 90th day of observation, it was established that in the Leydig cells, minor destructive disturbances in the ultrastructural organization of the lamellar cytoplasmic Golgi complex were detected. In some cells, 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 loose, thickened, and had a high electron density. A small number of cells had fragmented smooth endoplasmic reticulum. Hyaloplasm of glandulocytes was significantly brightened and contained very few free ribosomes and polysomes, in comparison with the control group of animals and with the previous term. In the cytoplasm, there are few mitochondria, they are single, but different in size and shape, the matrix of which is not detected, single cristae are found (Fig. 2).

The 180th day of observation was characterized by a significant decrease in the number of endocrinocytes in the interstitial lumen of convoluted tubules. A small number of cells with signs of destruction of the nucleus and cytoplasm are found in the interstitial tissue. The cells contain many pinocytotic vesicles, and the cytolemma forms pinocytotic intussusceptions, especially on the vascular surface. Neighboring endocrinocytes may have been disconnected from each other. The cells are characterized by the presence of a large cytoplasm, in which the smooth endoplasmic reticulum is well developed, which evenly fills the entire cytoplasm, and the rough endoplasmic reticulum is represented by separate short, widely anastomosing with each other. The share of agranular endoplasmic reticulum in the cells of a number of cells can reach 50 % or more. Nucleoli are not found in the nuclei of cells. Centrioles are rarely detected in cells, in those cells where they are detected, they are usually adjacent to the Golgi complex. Lipid inclusions and a low number of lysosomes are also found in endocrinocytes. The above-described

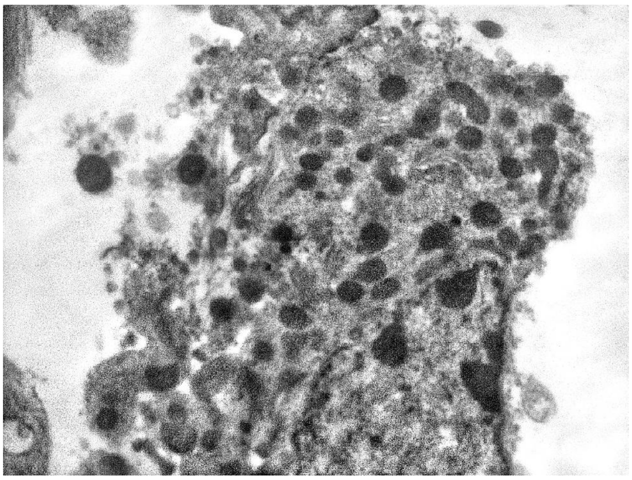

Fig. 3. Lipid inclusions of the endocrinocyte of the testis stroma on the 180th day of observation. x12 000.

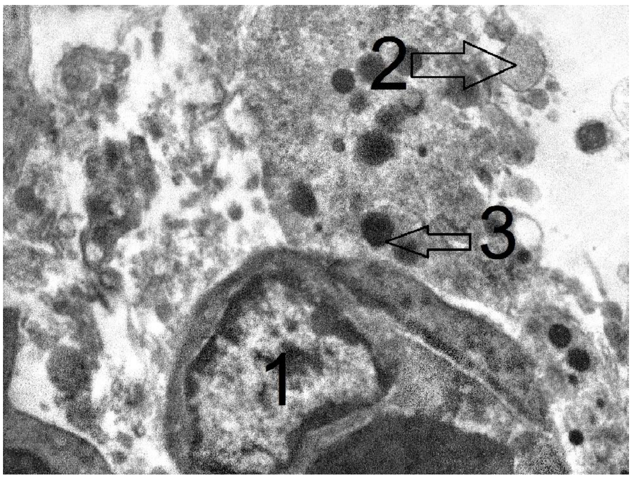

Fig. 4. Endocrinocyte of the stroma of the testis on the 270th day of observation. 1 - endocrinocyte nucleus, 2 - Reinke crystals, 3 - lipid inclusions. x12 000.

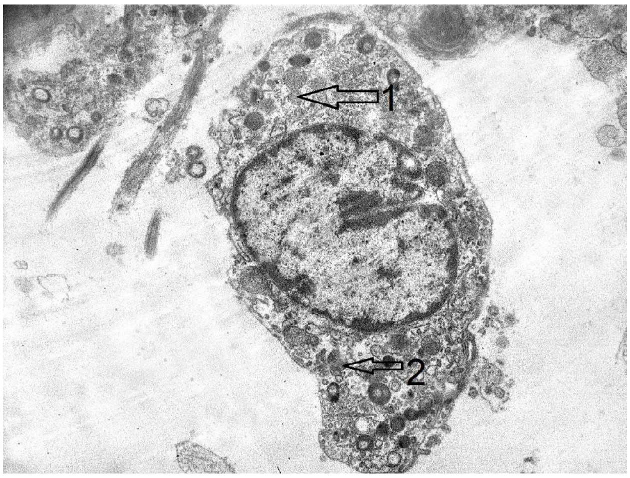

Fig. 5. Endocrinocyte of the stroma of the testis on the 365th day of observation. 1 - intracellular Reinke crystals, 2 - mitochondria. x9 000.

state of interstitial endocrinocytes was observed in opposition to active spermatogenesis in convoluted seminiferous tubules (Fig. 3).

The 270th day of observation was characterized by a decrease in the number of endocrinocytes, single cells near blood capillaries. A large number of cells (endocrinocytes, fibroblasts, macrophages) with signs of destruction are found in the interstitial tissue. These cells are relatively small, flat or polygonal in shape, with acidophilic cytoplasm, vacuolated on the periphery, smooth endoplasmic reticulum is not detected, single mitochondria of rounded shape. In the cytoplasm of endocrinocytes, the hexon-shaped prisms, with well-defined edges and corners, formations in the form of a "wasp's nest" - Reinke crystals (which are layering resulting from the disintegration of the membranes of the smooth endoplasmic reticulum) are sometimes determined (Fig. 4).

In the studied animals, on the 365th day, fibrosis of the interstitial connective tissue of convoluted tubules was detected. The number of vessels is increased. Endocrinocytes are small in size, single. In the cytoplasm of which single lipid granules, endoplasmic reticulum and Golgi complex are poorly developed. Core of normal size, light-optical. Nucleoli are absent. Mitochondria are round, single. We found the presence of Reinke crystals in the cytoplasm of interstitial endocrinocytes and outside the borders of the cells themselves (Fig. 5).

Discussion

The differences we identified in the morphological parameters of endocrinocytes at different observation periods when triptorelin was administered obviously indicate that triptorelin causes increasing destructive disturbances in the ultrastructural organization of these cells, which are manifested by different pathological stages and the degree of their functional activity of the internal components of the cell. The analysis of the structure of the population of interstitial endocrinocytes showed that the basis of the population of these testicular cells is rounded, oval or polygonal cells of medium size with a well-developed cytoplasm, medium, sometimes large nuclei. These are mature differentiated cells that, as a result of determination and differentiation, have acquired clearly expressed specialization, the ability to synthesize androgens. These cells have a well-developed smooth endoplasmic reticulum, numerous mitochondria, and lipid droplets can be detected in the cytoplasm. Small, spindle-shaped cells, similar in some structural features to fibroblasts, are the youngest and least differentiated cells. They are probably the source of maintaining the constancy of cell composition in this population. It is known that no mitotic activity was detected in the pubertal population of endocrinocytes, as evidenced by our results and literature data [1, 2, 6, 9]. Therefore, stability in the population is ensured by a dynamic balance between the processes of differentiation of endocrinocytes from their poorly differentiated precursors and the processes of their death. The rat endocrinocyte population belongs to cell populations of a stable type. This is evidenced by the fact that no mitoses were detected among the interstitial endocrinocytes of the testes in any of the sexually mature rats studied by us. The great diversity in the content of lipid inclusions in the cytoplasm of interstitial endocrinocytes of different mammals is caused by several factors. For example, according to other data [20], animals in which seasonality in reproductive activity is not expressed, as a rule, have few liposomes in the cytoplasm of interstitial endocrinocytes, lipid droplets of different (both low and high) electron density are found in the cytoplasm, and in the content of lipid inclusions in these animals varies little depending on sexual activity. Animals that do not exhibit seasonality in reproduction usually contain few lipid inclusions in the cytoplasm of endocrinocytes. On the contrary, in animals with a seasonal nature of reproduction, many lipid droplets of different electron density, surrounded by a membrane, are almost always found in the cytoplasm of such cells. Our data on this issue confirm the information available in the literature [14, 19]. It should be noted that the number of secretory inclusions is no longer an indicator that clearly indicates a low or high level of steroidogenesis in cells. A large amount of a secretory product in a cell can be: a) an indicator of a delay in the secretory process at the stage of secretion removal; b) an indicator of high functional activity. The latter is observed if the agranular endoplasmic reticulum in the cells is well developed, mitochondria are numerous, frequent contacts of mitochondria with smooth endoplasmic reticulum vesicles and lipid droplets. An important role in the analysis of morphological equivalents of steroidogenesis can be played by counting the number of mitochondria, but also by taking into account the peculiarities of the structure of mitochondrial structures. Thus, tubulovesicular cristae in mitochondria are characteristic of steroid-producing cells. Therefore, the presence of a large number of mitochondria with tubulovesicular cristae is one of the indicators of active steroidogenesis. Interstitial endocrinocytes of testes may contain pigment inclusions in the cytoplasm. Among the rats we studied, the highest content of pigment inclusions in the cytoplasm of interstitial endocrinocytes was not noted. The frequency of finding Reinke's crystals, their number and volume of the crystal in relation to the volume of the cell correlates with age, increasing in the older age group [1, 17], as is known from the literature. Correlation with the level of testosterone was not found in the literature, which allows to mark Reinke crystals as a product of degenerative processes in the cell [10], which can also be indirectly evidenced by an increase, as well as their number in testicular biopsies from subjects with cryptorchidism [2, 12]. Therefore, the presence of these crystals in our experiment with the introduction of triptorelin in the interstitial cells and in the pericellular space indicates the cessation of androgen synthesis in them and intrinsic degenerative changes in the cells.

The results obtained by us are a theoretical justification for the development of methods for correcting violations of the generative and endocrine function of the testicles in the case of pathological effects on the body, with damage to endo- and paracrine regulations. Data on the functional morphology of the testes at the stages of adaptation to changes in the endocrine and immune function of the testes expand the existing understanding of the causes of spermatogenesis disorders and its regulation.

Conclusions

1. Long-term administration of triptorelin causes hormonal dysregulation in the hypothalamus-pituitary-testis system, which leads to quantitative and qualitative changes in the population of endocrine cells in the interstitial space of the testis, which is confirmed by electron microscopic changes in subcellular structures.

2. The maximum effect of triptorelin is determined from the 180th day of observation, which is characterized by an increase in degenerative changes in endocrinocytes, and the detection of Reinke crystals in the cytoplasm of interstitial endocrinocytes from the 270th day of observation.

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ЕЛЕКТРОННОМІКРОСКОПІЧНІ ЗМІНИ В ІНТЕРСТИЦІЙНИХ ЕНДОКРИНОЦИТАХ СІМ'ЯНИКІВ ЩУРІВ ПРИ ВВЕДЕННІ ТРИПТОРЕЛІНУ ПРОТЯГОМ 365 ДІБ

Стецук Є. В., Шепитько В. І., Борута Н. В., Вільхова О. В., Скотаренко Т. А., Рудь М. В.

Трипторелін є агоністом гонадотропін-рилізинг-гормону, який є потужним інгібітором синтезу тестостерону (у чоловіків) та естрогену (у жінок) і використовується для лікування прогресуючого раку простати. Дослідження механізмів регуляції та синтезу утворення тестостерону в тестикулярних інтерстиційних клітинах демонструють численні ендогенні мішені, які можуть збільшити біосинтез тестостерону, що може пом'якшити ефекти зниження тестостерону. Трипторелін, синтетичний аналог нейрогормону гонадоліберину, пригнічує експресію рецептора GnRH в гіпофізі, але не змінює функціонування гіпофізарно-тестикулярного комплексу. Мета дослідження - вивчити електронномікроскопічні зміни інтерстиціальних ендокриноцитів сім'яників щурів після введення трипторeліну протягом 365 діб. Експеримент проведено на 35 статевозрілих самцях білих щурів. Щури були поділені на 2 групи: контрольна група (І) - вводили фізіологічний розчин, ІІ група з центральною депривацією синтезу лютеїнізуючого гормону - підшкірно вводили трипторелін у дозі 0,3 мг діючої речовини на кг маси тіла щура. Проведене дослідження інтерстиційного простору в сім'яниках білих щурів показало, що довготривале введення трипторeліну викликає гормональну дисрегуляцію за системою гіпоталамус-гіпофіз-яєчко, що призводить до кількісних та якісних змін в ендокринних клітинах інтерстиційного простору яєчка, яке підтверджується електронномікроскопічними змінами субклітинних структур. Максимальний вплив трипторeліну визначається з 180-ї доби спостереження, що характеризується підвищенням дегенеративних змін в ендокриноцитах та виявленням з 270-ї доби спостереження кристалів Рейнке в цитоплазмі інтерстиційних ендокриноцитів.

Ключові слова: *сім'яники, електронна мікроскопія, щури, інтерстиційні ендокриноцити, лютеїнізуючий гормон, трипторелін.*

Author's contribution

Stetsuk Ye. V.: work concept and design, data collection and analysis, responsibility for statistical analysis, writing the article.
Shepytko V. I.: final approval of the article.
Boruta N. V.: responsibility for statistical analysis.
Vilkhova O. V.: work concept and design.
Skotarenko T. A.: writing the article.
Rud M. V.: writing the article.