Журнал «Перспективи та інновації науки»
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# ULTRASTRUCTURAL CHANGES IN THE LIVER OF RATS UNDER THE ACTION OF VIPERA BERUS BERUS VENOM

**Abstract.** The study and analysis of ultrastructural changes in the liver of rats under the influence of Vipera berus berus venom were conducted.

**The aim of the study.** To determine the ultrastructural changes in the liver of rats under the influence of Vipera berus berus venom.

**Materials and methods.** The study was conducted on white male rats. The venom of Vipera berus berus was obtained from the V. N. Karazin Kharkiv National University. The animals were divided into two groups (10 individuals) during the study: control and experimental. The experimental rats were intraperitoneally injected with a semi-lethal dose ($LD_{50}$) (1.576 $mg/g^{-1}$) of Vipera berus berus venom in a saline solution. The rats were removed from the experiment 24 hours after exposure to the venom and euthanised by cervical dislocation. Liver pieces 0.5-1 mm in size were fixed in a 2.5% glutaraldehyde solution. Then, they were injected into a mixture of upon-araldite according to the generally accepted method. Sections were made from the obtained blocks and stained with toluidine blue and Hayat. Ultrathin sections were examined and photographed under a PEM125K electron microscope with a magnification of 6-20 thousand times.

**Results of the study.** Electron microscopic study of the liver of experimental animals under the influence of Vipera berus berus venom showed significant changes in the ultrastructure of the parenchymal and vascular components. Most hepatocytes were characterised by moderately electron-dense hyalo- and karyoplasm with destructive changes in the nucleus and organelles. However, more often than in the control group, “light” hepatocytes were found, which contained sharply electron-bright hyaloplasm and single membrane organelles that were indistinct and fragmented. The hemotoxic effect of the venom of the Vipera berus berus caused an increase in the number of Kupffer cells, which lost their connection with the endothelium and migrated into the perisinusoidal space. The presence of numerous primary and secondary, voluminous phagosomes in the cytoplasm was characteristic of them.

**Conclusions.** The results of the electron microscopic study of the liver of experimental animals under the influence of Vipera berus berus venom showed significant violations of the ultrastructure of the vascular and parenchymal

components of the organ. The toxic effect of the venom, which has a vascular genesis, caused direct damage to the ultrastructure of the vascular wall, in particular sinusoids, and therefore, a significant alteration of the nuclei and cytoplasm of hepatocytes. As a manifestation of the organ's protective mechanisms against toxic damage, the number of active macrophage Kupffer cells and pit cells increased.

**Keywords:** venom, vipers, liver, rats.

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## УЛЬТРАСТРУКТУРНІ ЗМІНИ ПЕЧІНКИ ЩУРІВ ЗА УМОВ ДІЇ ОТРУТИ ГАДЮКИ VIPERA BERUS BERUS

**Анотація.** Проведено дослідження та аналіз ультраструктурних змін печінки щурів за умов дії отрути гадюки Vipera berus berus.

**Мета дослідження.** Визначити ультраструктурні зміни печінки щурів за умов дії отрути гадюк Vipera berus berus.

**Матеріали та методи.** Дослідження проводилось на білих щурах-самцях.

Отруту Vipera berus berus отримано з Харківського національного університету імені В. Н. Каразіна. Тварин в ході дослідження розділили на дві групи по 10 особин: контрольну та дослідну. Піддослідним щурам внутрішньоочеревинно вводили напівлетальну дозу ($LD_{50}$) (1,576 мг/г$^{-1}$) отрути Vipera berus berus у фізіологічному розчині. Щури були виведені з експерименту через 24 години після впливу отрути, знеживлюючи шляхом цервікальної дислокації. Шматочки печінки розміром 0,5-1 мм фіксували в 2,5% розчині глутаральдегіду. Далі їх вводили в суміш епон-аральдиту за загальноприйнятою методикою. З отриманих блоків виготовляли зрізи, які фарбували толуїдиновим синім і Hayat. Ультратонкі зрізи досліджували та фотографували під електронним мікроскопом PEM125K зі збільшенням в 6-20 тисяч разів.

**Результати дослідження.** Електронномікроскопічне вивчення печінки експериментальних тварин за умов впливу отрути гадюки Vipera berus berus показало значні зміни ультраструктури паренхіматозного та судинного компонентів. Переважна більшість гепатоцитів характеризувалась помірно електроннощільною гіало- та каріоплазмою із деструктивними змінами ядра та органел. Однак частіше ніж в контрольній групі виявлялись “світлі” гепатоцити, які містили різко електронносвітлу гіалоплазму, поодинокі мембранні органели, які були нечіткими та фрагментованими. Гемотоксичний вплив отрути гадюки Vipera berus berus спричинив зростання кількості клітин Купфера, які втрачали зв'язок із ендотелієм та мігрували в перисинусоїдний

Журнал «Перспективи та інновації науки»
(Серія «Педагогіка», Серія «Психологія», Серія «Медицина»)
№ 1(47) 2025

простір. Для них характерною була наявність в цитоплазмі чисельних первинних та вторинних, об'ємних фагосом.

**Висновки.** Результати проведеного електронномікроскопічного вивчення печінки дослідних тварин за умов дії отрути гадюки Vipera berus berus показали значні порушення ультраструктури судинного та паренхіматозного компонентів органу. Токсичний вплив отрути, що носить судинний генез, зумовив пряме пошкодження ультраструктури стінки судин, зокрема синусоїдів, а відтак і значну альтерацію ядер і цитоплазми гепатоцитів. Як прояв захисних механізмів органу на токсичне пошкодження зросло число активних макрофагальних клітин Купфера та pit-клітин.

**Ключові слова:** отрута, гадюки, печінка, щури.

**Statement of the problem.** Due to the significant distribution of poisonous animals, humanity is in constant contact with them, which often causes poisoning, serious injuries or fatal consequences. Snakes, vipers, spiders and scorpions are most often found among the entire variety of poisonous animals. According to literary sources, about 1.8-2.7 million cases of snakebites are recorded annually, leading to 81,000 - 138,000 deaths of victims, and 100,000 of them are characterised by the development of irreversible physical or mental disorders. The most common poisonings due to snake and viper bites are in Asia, Africa, sub-Saharan Africa and Latin America. Such a wide distribution and a significant percentage of mortality cause the growing attention of the scientific community to this problem. In particular, the WHO has included snakebite poisoning in the list of neglected tropical diseases [1, 2, 3, 4]. In some regions of the world, scorpion poisoning is a pressing health problem, with up to 1.2 million cases per year, resulting in the death of more than 3,000 victims [5].

**Connection of the publication with planned scientific research works.** It has been established that toxic substances exhibit a wide range of pathological effects on most vital systems, causing damage to the lungs, heart, kidneys, skeletal muscles, etc. [6, 7, 8, 9]. However, the number of experimental studies on the influence of the venom of various species of snakes and vipers on morpho-functional changes in the liver is very limited. It is undeniable that the liver occupies one of the main places in the detoxification of exogenous and endogenous toxic compounds. In modern conditions of the world, the human body is in constant contact with toxicants of various origins, and the ability of the liver to quickly utilize them determines, in a certain way, the ability to survive and maintain homeostasis parameters at a relatively constant level. However, during the metabolism of many xenobiotics, including poisons of animal origin, irreversible changes in the features of the histological organisation and the course of biochemical processes in liver cells are possible, which ultimately leads to its dysfunction as a whole, and in severe cases to the development

of toxic necrosis. Scientists suggest that this condition occurs due to the formation of toxic metabolites during detoxification, which have a detrimental effect on the molecular structures of hepatocytes, causing their death [10]. Asmari A. K. et al. [11] studied serological markers of acute hepatotoxicity caused by the action of Echys pyramidum snake venom in rats. 3-6 hours after its intraperitoneal administration to experimental animals, pronounced changes in the functional activity of the organ were detected. According to some studies, toxins of Crotalus durissus terrificus vipers cause the development of acute liver damage. The results of studies by Ghosh R. and co-authors [12] on the hepatotoxicity of Vipera russelli venom confirmed the development of destructive-dystrophic changes in the structure of the liver under the conditions of its administration to experimental animals. Al-Quraishy et al. [13], studying the effect of Naja haje snake venom on the structural and functional parameters of the liver of laboratory rats, proved its hepatotoxic effect and ability to cause the development of OS.

**The purpose of the article** is to determine ultrastructural changes in the liver of rats under the influence of the venom of the viper Vipera berus berus.

**Research objects and methods.** The study was conducted on male white rats. The rats underwent a thorough 7-day acclimatisation in a special animal facility at Taras Shevchenko National University of Kyiv. This was followed by transfer to laboratory conditions with strict adherence to temperature and light regimes [14]. The experiment was conducted by the Recommendations of the National Institute of Health for the Care and Use of Laboratory Animals and the European Council Directive of November 24, 1986, on the Care and Use of Laboratory Animals (86/609/EEC). The study was approved and confirmed by the Bioethics Commission of the Institute of Biology and Medicine of Taras Shevchenko National University of Kyiv (protocol No. 2, dated August 19, 2021). Vipera berus berus venom was obtained from V. N. Karazin Kharkiv National University. The lyophilised native venom was carefully stored at -20°C and dissolved in saline immediately before the experiment, ensuring our study's highest scientific accuracy and reliability.

Animals were divided into two groups of 10 individuals: control and experimental. In saline, experimental rats were intraperitoneally injected with a semi-lethal dose ($LD_{50}$) (1.576 mg/$g^{-1}$) of Vipera berus berus venom. Animals in the control group were intraperitoneally injected with saline only. Rats were removed from the experiment 24 hours after exposure to the venom and euthanised by cervical dislocation.

Liver slices 0.5-1 mm in size were fixed in 2.5% glutaraldehyde solution in phosphate buffer pH 7.2-7.4. Then, they were introduced into the Epon-Araldite mixture according to the generally accepted method [15, 16]. Sections were made from the obtained blocks and stained with toluidine blue and Hayat. After field microscopy of thin sections, ultrathin sections were made using LKB III (Sweden)

Журнал «Перспективи та інновації науки»
(Серія «Педагогіка», Серія «Психологія», Серія «Медицина»)
№ 1(47) 2025

and Reihart (Austria) ultramicrotomes, which were contrasted with a 2% solution of uranyl acetate and lead citrate. The sections were examined and photographed under a PEM125K electron microscope with a magnification of 6-20 thousand times.

**Presentation of the main material.**

**Research results and their discussion.** Electron microscopic study of the liver of experimental animals exposed to the viper Vipera berus berus venom showed significant changes in the ultrastructure of the parenchymal and vascular components. The plasmalemma of hepatocytes was indistinct in many areas, and the integrity of intercellular contacts was lost. Bile capillaries were poorly contoured with few microvilli. (Fig. 1).

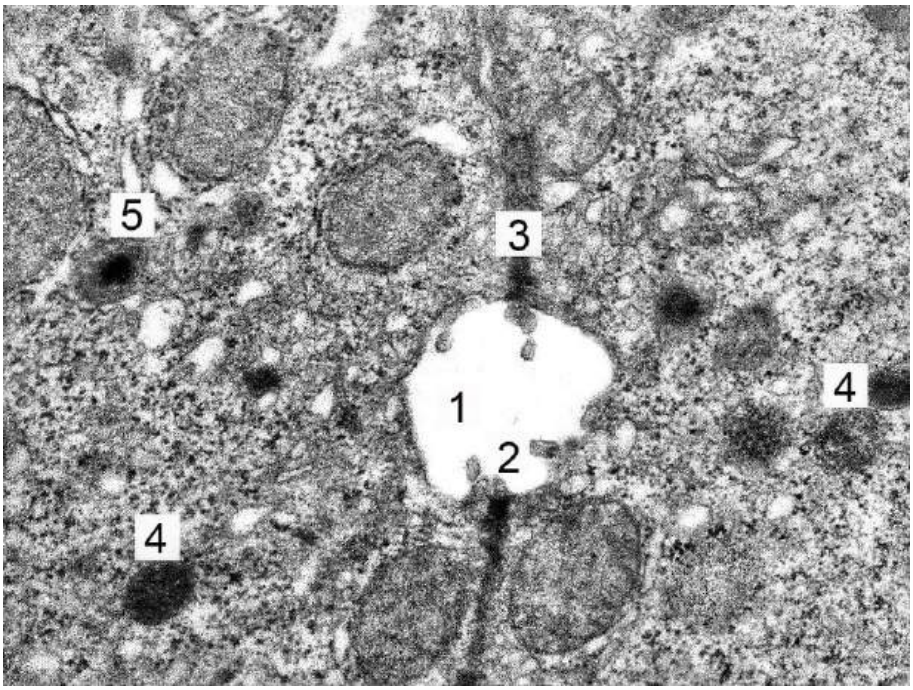


*Fig. 1. Ultrastructural changes in the bile capillary of animals under the influence of the viper Vipera berus berus. Destructured, dilated bile capillary lumen (1), single microvilli (2), indistinct tight junction (3), osmiophilic lysosomes (4), and peroxisomes (5). x 17,000*

The cell nuclei were round, partially deformed, with minor invaginations of the karyolemma, which were indistinct. The perinuclear space was locally expanded. The nucleus contained mainly electron-bright euchromatin, but large heterochromatin clusters were marginally defined. The nucleoli were small and osmiophilic, and nuclei without nucleoli were observed. The number of binucleated cells decreased. Functional tension in the organ under the toxic effects of the poison of the steppe viper was accompanied by heterogeneity of hepatocytes. The appearance of numerous “dark” cells was determined, in which the cytoplasm of increased osmiophilicity contained poorly developed organelles of the synthetic and energy apparatus, which were largely destructured. The endoplasmic reticulum was formed

by short, locally thick tubules, voluminous vacuoles, and single vesicles. The Golgi complex cisternae are poorly contoured and localised paranuclearly. The number of osmiophilic primary lysosomes, secondary phagosomes and peroxisomes increases. The content of finely dispersed, osmiophilic glycogen inclusions decreases. Mitochondria are mainly small, electron-dense, with reduced cristae. Large loci of moderate osmiophilicity were observed in the cytoplasm of such hepatocytes, devoid of organelles and inclusions. (рис. 2).

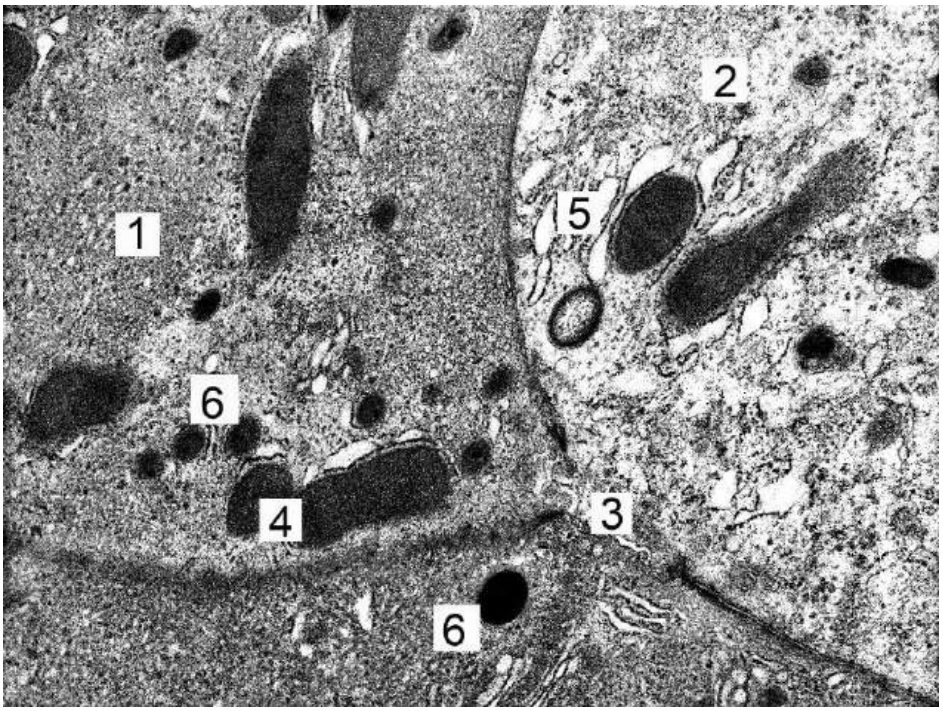


*Fig. 2. Ultrastructural changes in hepatocytes of animal livers under the influence of the viper Vipera berus berus. Osmiophilic hyaloplasm of a "dark" hepatocyte (1), a fragment of a hepatocyte with the cytoplasm of moderate osmiophilic (2), the indistinct lumen of a bile capillary (3), osmiophilic mitochondria (4), short, dilated tubules of the granular endoplasmic reticulum (5), osmiophilic lysosomes (6). x 12,000*

Most hepatocytes were characterised by moderately electron-dense hyalo- and karyoplasm with destructive changes in the nucleus and organelles. However, more often than in the control group, "light" hepatocytes were found, which contained sharply electron-bright hyaloplasm and single membrane organelles that were indistinct and fragmented. (Fig. 3).

Журнал «Перспективи та інновації науки»
(Серія «Педагогіка», Серія «Психологія», Серія «Медицина»)
№ 1(47) 2025

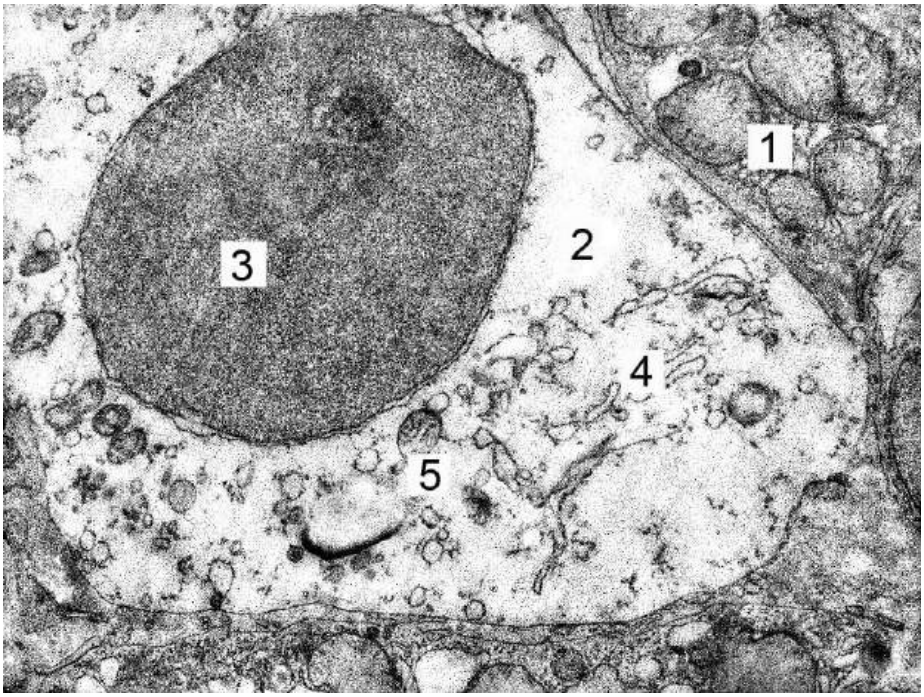


*Fig. 3. Ultrastructural changes in hepatocytes of animal livers under the influence of the viper Vipera berus berus. Electron-dense hyaloplasm of a "dark" hepatocyte (1), hyaloplasm of a "light" hepatocyte (2), nucleus (3), tubules of the granular endoplasmic reticulum (4), mitochondria (5). x 1 5000*

The hemotoxic effect of the viper Vipera berus berus venom caused an increase in the number of Kupffer cells, which lost their connection with the endothelium and migrated into the perisinusoidal space. They were characterised by numerous primary and secondary, voluminous phagosomes in the cytoplasm. The organelles in the cytoplasm were poorly expressed and damaged, and non-extending tubules of the endoplasmic reticulum were determined. The cell nucleus was round, heterochromatin prevailed in the karyoplasm, the karyolemma was indistinct, and nuclear pores were not determined (Fig. 4). During this period of observation, the number of pit cells in the perisinusoidal space of Disse increased as a manifestation of protective immune reactions. A characteristic feature of these cells is the presence of a round, heterochromatin nucleus, a small area of cytoplasm with moderately developed organelles. Endoplasmic reticulum tubules, electron-dense, specific granules, and osmiophilic lysosomes were often identified in the cytoplasm, as these cells act as natural killers (Fig. 5). Ito cells with inclusions of lipid granules in the cytoplasm were also identified.

Журнал «Перспективи та інновації науки»
(Серія «Педагогіка», Серія «Психологія», Серія «Медицина»)
№ 1(47) 2025

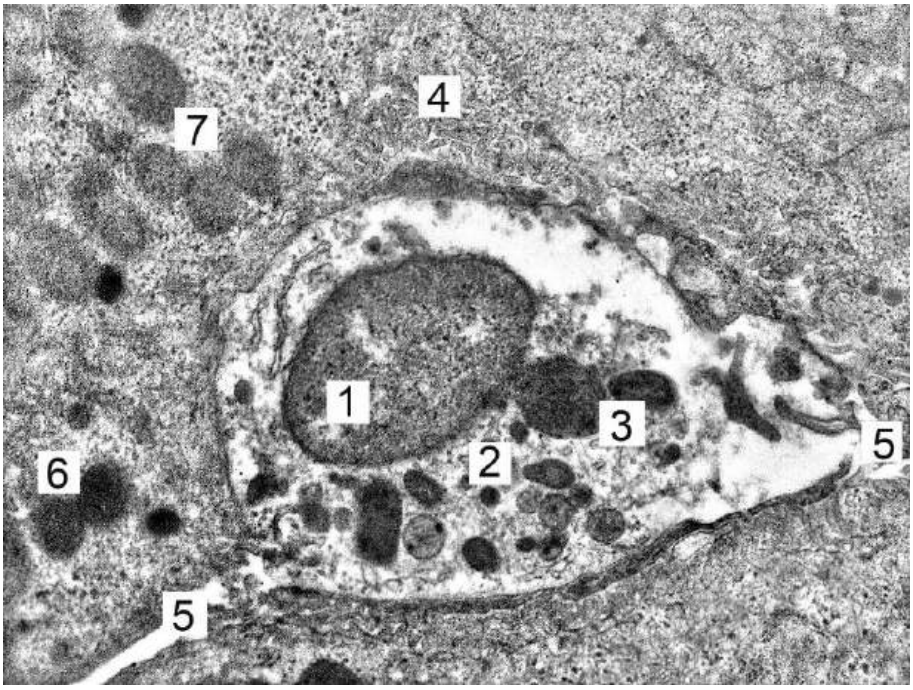


*Fig. 4. Submicroscopic changes in the liver of animals exposed to the viper Vipera berus berus. Macrophage nucleus (1), primary lysosomes (2), secondary lysosomes, phagosomes (3), microvilli in the perisinusoidal space of Disse (4), damaged intercellular contacts (5), lysosomes (6), homogeneous mitochondria with damaged membranes (7). x 11,000*

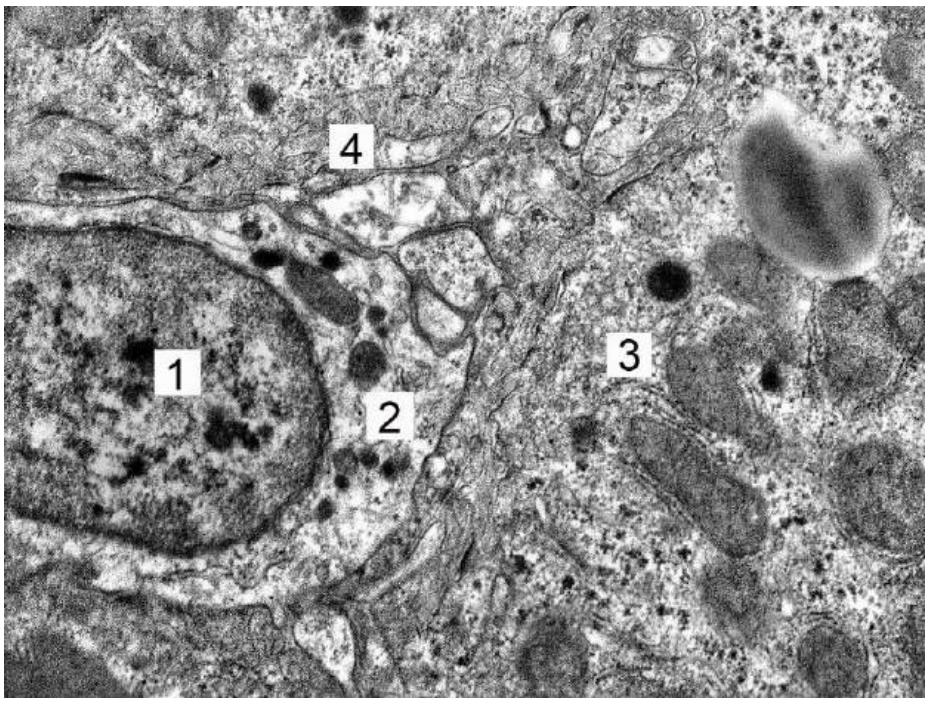


*Fig. 5. Submicroscopic changes in hepatocytes of animal livers under the influence of the viper Vipera berus berus. Pit cell nucleus with osmiophilic clumps of heterochromatin (1), narrow cytoplasm and specific electron-dense granules (2), hepatocyte fragment (3), destructured perisinusoidal space (4). x 13,000*

Журнал «Перспективи та інновації науки»
(Серія «Педагогіка», Серія «Психологія», Серія «Медицина»)
№ 1(47) 2025

Dyscirculatory changes in the organ under the toxic effects of the poison of the steppe viper were manifested by narrowed or mainly dilated sinusoidal hemocapillaries. Such dilated, full-blooded hemocapillaries contained erythrocytes, platelets, and leukocytes, in particular monocytes, which transform into mature macrophages to ensure the protective functions of the liver under the toxic effects of the poison of the steppe viper. The capillary wall is vaguely contoured, and the basement membrane is discontinuous with wide pores and is absent in significant areas. It often forms osmiophilic homogeneous stripes (Fig. 6). Endothelial cells lining the hemocapillaries mainly had an oval, elongated heterochromatin nucleus with an indistinct karyolemma. Local oedema of the cytoplasmic areas of the cells is detected, and the lumenal surface of the plasmalemma was also vaguely structured (Fig. 7).

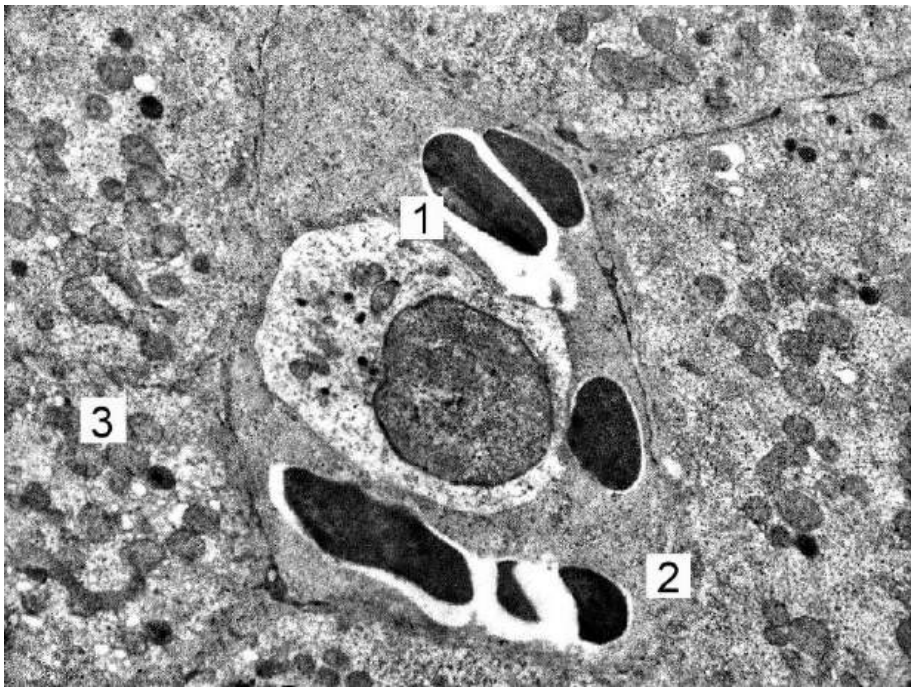


*Fig. 6. Submicroscopic changes in the liver of an animal exposed to the viper Vipera berus berus. Dilated hemocapillary lumen with formed blood elements (1), fragmented, homogeneous capillary wall (2), hepatocyte cytoplasm (3). x 12,000*

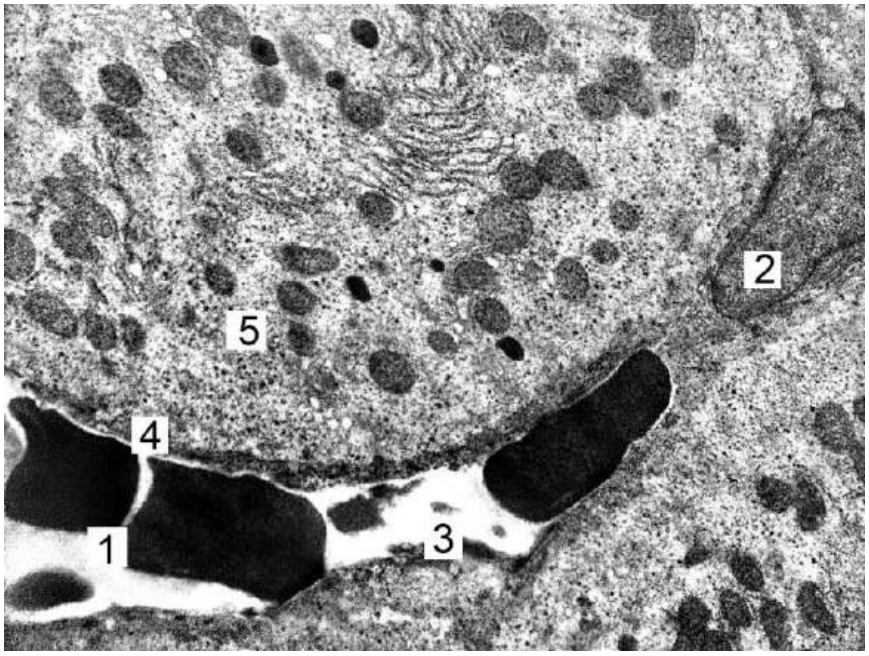


*Fig. 7. Submicroscopic changes in the liver of an animal exposed to the viper Vipera berus berus. The lumen of a hemocapillary with erythrocytes (1), the nucleus of an endothelial cell (2), the destructively altered capillary wall (3), the homogeneous, osmiophilic perisinusoidal space of Disse (4), a fragment of a hepatocyte (5). x 13,000*

**Conclusions**. The results of the electron microscopic study of the liver of experimental animals under the influence of the venom of the viper Vipera berus berus showed significant violations of the ultrastructure of the vascular and parenchymal components of the organ. The toxic effect of the venom, which has a vascular genesis, caused direct damage to the ultrastructure of the vascular wall, in particular sinusoids, and, therefore, a significant alteration of the nuclei and cytoplasm of hepatocytes. As a manifestation of the organ's protective mechanisms against toxic damage, the number of active macrophage Kupffer cells and pit cells increased.

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