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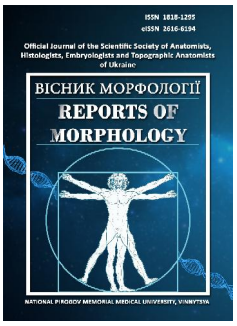

Structural changes in the heart tissue of rats under conditions of acute intoxication with Vipera berus berus venom

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Among all poisonous animals, snakes attract the special attention of mankind. Cases of poisoning by their toxins are extremely common and are an unsolved public health problem worldwide. It has been established that among a number of complications due to snakebites, an important role is played by disturbances in the normal functioning of the organs of the cardiovascular system. The aim of the research is to study the features of histological changes in the heart tissue of rats under conditions of acute intoxication with Vipera berus berus venom. Experimental studies were carried out on white non-linear male rats. The animals were conditionally divided into two groups - a control and an experimental group of 10 individuals each. Experimental rats were injected intraperitoneally with a semi-lethal dose (LD50) (1.576 mg/g^{-1}) of Vipera berus berus venom in saline solution. Animals of the control group were injected intraperitoneally with only saline solution. Rats were removed from the experiment 24 hours after exposure to the venom, anesthetized by cervical dislocation. Heart samples were taken for microscopic examination. Fixation of the material and preparation of paraffin blocks were carried out according to generally accepted methods. Histological heart preparations were stained with Picro Sirius Red/Fast Green. Histological preparations were studied using a SEO SCAN light microscope. Thus, under the conditions of acute intoxication with Vipera berus berus venom in experimental rats, microscopic examination of the heart tissue revealed pathological shifts in the structural organization of all layers of the organ. In the epicardium, an increase in the volume of collagen fibers and thickening of vessel walls were characteristic. The most pronounced histological changes were observed in the myocardium. Swelling, disorganization of muscle fibers, their fragmentation, lysis, destruction, loss of characteristic transverse striations, necrosis were detected in it. In addition, an increase in the number of fibroblasts, their activation and, as a result, the growth of connective tissue components, including collagen fibers, in the myocardial tissue were revealed. The endocardium of experimental rats was distinguished by desquamation of the endothelial lining and an increase in the number of active fibroblasts in the outer connective tissue layer.

Keywords: *vipera, venom, heart, fibroblasts, destruction, rats.*

Introduction

Among all poisonous animals, snakes attract the special attention of mankind. On the one hand, this interest is due to the fact that cases of poisoning by their toxins are extremely common and belong to unsolved health problems worldwide, as they cause numerous fatal consequences. According to WHO estimates, 81,000 to 138,000 people die from snake bites every year, and another 400,000 victims have severe complications or even disability [8, 9, 10]. However, despite this, snake toxins are also considered valuable sources for the production of various medicines [2, 12]. Snakes use their venom to neutralize prey and to scare or weaken predators. The realization of these goals is possible due to the fact that toxins cause the development of muscle paralysis (by blocking the transmission of nerve impulses), cause changes in the functioning of the cardiovascular system, or cause pronounced local lesions at the sites of bites.

Snake venom is a mixture of enzymes and proteins without catalytic properties. The main enzymes include metalloproteinases (SVMPs), phospholipases A2 (PLA2), serine proteases (SVSPs), acetylcholinesterase, L-amino

acid oxidases (LAAOs), hyaluronidase, and nucleotidase [7, 20]. Proteins with non-enzymatic properties include three-finger toxins (3FTXs), C-type lectin-like peptides, natriuretic factor, proteinase inhibitors, and bradykinin-potentiating peptides (BPP) [3, 4, 19]. According to the literature, the composition of snake venom is not stable and may vary depending on sex, features of ontogenesis, geographic distribution, and environmental conditions [27]. Therefore, the compounds of their toxins are able to cause a number of biological effects both at the local and systemic levels [5]. It is known that severe pain, swelling and tissue necrosis usually occur at the site of venom inoculation [11]. At the level of organs and systems, the venom causes neuro-, myo-, cardio-, nephrotoxic effects, coagulopathy [1]. Such life-threatening complications force scientists to investigate in more detail the components of snake toxins in order to develop effective treatment methods.

The aim of the research is to study the features of histological changes in the tissue of the heart of rats under the conditions of acute intoxication with the venom of Vipera berus berus.

Materials and methods

Experimental studies were carried out on white non-linear male rats. For preliminary acclimatization, the animals were kept for 7 days in the animal facility of Taras Shevchenko National University of Kyiv, and then kept in laboratory conditions at constant temperature (22±3°C), humidity (60± 5 %) and light (12 h light/12 h dark cycle), being fed standard rodent food and water ad libitum. All experiments were conducted in accordance with the National Institutes of Health Guidelines for the care and use of laboratory animals and the European Council Directive of 24 November 1986 for the Care and Use of Laboratory Animals (86/609/EEC). The research was approved and confirmed by the Bioethics Commission of the NSC "Institute of Biology and Medicine" of the Taras Shevchenko National University of Kyiv (protocol No. 2 dated August 19, 2021).

Vipera berus berus venom was obtained from the V. N. Karazin Kharkiv National University. The lyophilized crude venom was stored at -20°C and then dissolved in saline solution immediately before the experiment.

The animals were conditionally divided into two groups - a control and an experimental group of 10 individuals each. Experimental rats were injected intraperitoneally with a semi-lethal dose (LD50) (1.576 mg/g^{-1}) of Vipera berus berus venom in saline solution. Animals of the control group were injected intraperitoneally with only saline solution. Rats were removed from the experiment 24 hours after exposure to the venom, anesthetized by cervical dislocation.

Heart samples were taken from pre-weighed animals of all groups for microscopic examination. The pieces were fixed in a 10 % formalin solution, while the duration of exposure did not exceed 1-2 days. The applied fixing solution prevents the process of autolysis and stabilizes cells and tissues for their further processing and use in staining procedures. Next, the pieces were dehydrated in alcohols of increasing concentration and embedded in paraffin blocks. Staining of histological preparations of hearts was performed according to the Picro Sirius Red/Fast Green method [21]. Histological preparations were studied using a SEO SCAN light microscope and photo-documented using a Vision CCD Camera with a system of image output from histological preparations.

Results

Under the conditions of acute intoxication with Vipera berus berus venom in the heart of experimental rats significant changes in the normal histostructure of all layers of the organ were observed. The composition of the epicardium was dominated by connective tissue elements, mainly collagen fibers, which, growing, formed a so-called mesh and later interwoven into the adjacent myocardial tissue. These fibers were subject to intensive dyeing. It should be noted that during microscopic examination, in addition to collagen fibers, which typically form the framework of this heart layer, an increase in the content of young fibers was noted. Against their background, the mesothelium layer was almost not visualized. The blood vessels of the epicardium had wide lumens. Deformation of the walls was observed in the arteries. The endothelial layer of their intima was thinned, subject to local detachment from the basement membrane into the vessel lumen, while in other areas, erythrocytes tightly adhered to the epithelial lining. Tunica media in the vast majority of arterial blood vessels of the epicardium consisted of a significant number of fibers and single smooth myocytes. The adventitia was thickened, collagenized. The arteries were characterized by signs of pronounced full blood, numerous erythrocytes and leukocytes were noted in their lumens (Fig. 1).

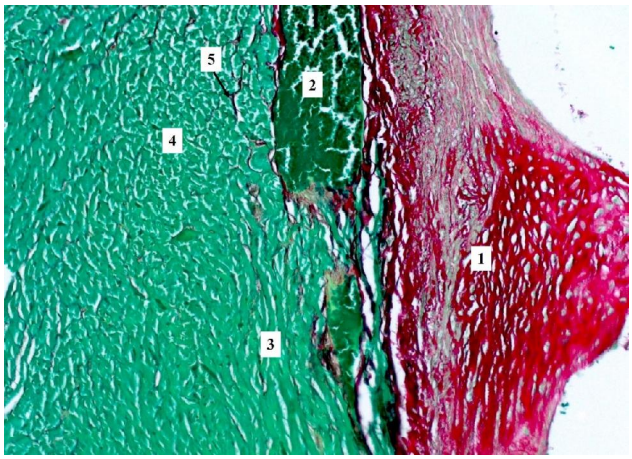

Fig. 1. Histological changes in the heart of rats under the conditions of exposure to Vipera berus berus venom. The growth of collagen fibers in the epicardium (1), the lumen of a blood vessel with formal elements (2), muscle fibers of the myocardium (3), cells of the conducting system of the heart (4), collagen fibers in the intermyofibrillar spaces (5). Picro Sirius Red/Fast Green. x200 magnification.

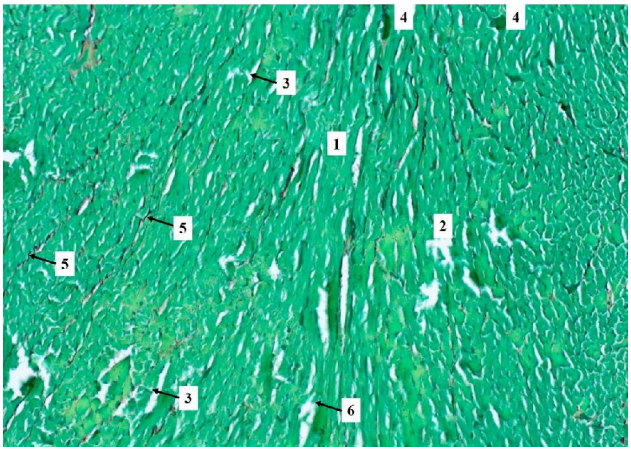

Fig. 2. Microscopic changes in the heart of rats exposed to Vipera berus berus venom. Thickening and swelling of muscle fibers (1), areas of myocardial tissue destruction (2), fragmentation of myocardial muscle fibers (3), areas of hemorrhage (4), collagen fibers (5), dissection of myocardial muscle fibers (6). Picro Sirius Red/Fast Green. x200 magification.

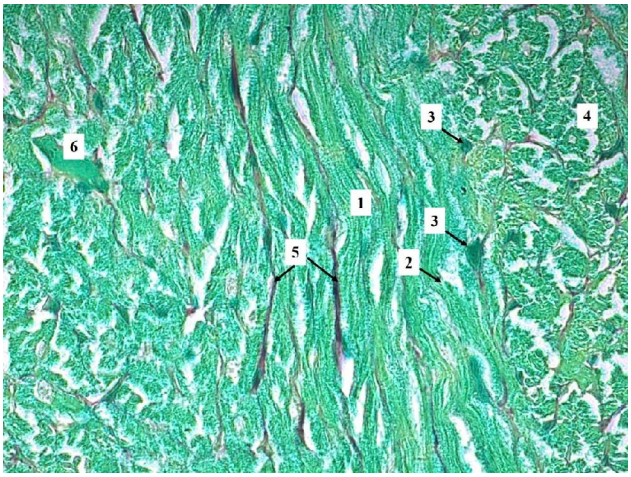

Fig. 3. Histological organization of the heart of rats under the influence of Vipera berus berus venom. Wave-like orientation of myocardial muscle fibers (1), sarcolemma destruction zone (2), fibroblasts (3), hydropic dystrophy of Purkinje cells (4), collagen fibers (5), blood vessel lumen (6). Picro Sirius Red/Fast Green. x1000 magnification.

In the myocardium of experimental animals, muscle fibers were swollen, lost their characteristic longitudinal orientation and acquired a winding shape. In most fields of view, zones of destruction of the sarcolemma were noted, and the transverse striation of the myocardial fibers was not clearly expressed. Zones of destruction of contractile elements and fragmentation of fibers were also determined in cardiac muscle tissue (Fig. 2). Between the latter, the volume of loose connective tissue increased significantly, the gaps between them widened. Contractile cardiomyocytes under these conditions lost their usual rectangular shape. Their nuclei could not be clearly visualized and identified in almost all fields of view due to severe swelling of the myocardial fibers. Some of them, which were able to be differentiated, were hypochromic, had an elongated shape. Also, due to the destruction of muscle fibers, some nuclei were outside the contractile cardiomyocytes. Intercalated discs had barely noticeable outlines on micropreparations. Zones of smoothing and lysis of muscle fibers were characteristic findings, as well as foci of necrosis. Cells of the leukocyte line were rarely recorded under the specified conditions, and therefore, myocardial infiltration during acute intoxication with Vipera berus berus venom is moderately pronounced.

The venom of Vipera berus berus in experimental rats caused a significant growth of collagen fibers in the tissue of the myocardium. Thus, the activation of fibroblasts, which were the main producers of components of loose connective tissue, including collagen fibers, was observed. Their number increased in the spaces between contractile and conducting cardiomyocytes. Fibroblasts had an elongated spindle-like or stellate shape. Against the background of cardiomyocytes, they were stained more intensively. Their nuclear-cytoplasmic index was high, which indicates the activity of synthetic processes in the cells. Fibroblast nuclei were located centrocentrically, were normochromic, chromatin had a diffuse distribution with a predominance of euchromatin. Under these conditions, the blood vessels of the myocardium of experimental animals were also subject to structural changes. The walls of the arteries thickened considerably. Endotheliocytes of the inner layer of the vessel wall had the appearance of palisades, protruding into the lumen of the arteries. Desquamation of the endothelial lining of the vascular wall from the components of the basement membrane was observed. In some histopreparations, loosening and swelling of the intima of the arteries were noted. The tunica media of arterial vessels was characterized by a pronounced increase in the number of collagen fibers, while the number of smooth muscle cells decreased. Most of the arteries had a thickened tunica adventitia. Myocardial vessels were full of blood, their lumens were filled with formal blood elements, namely erythrocytes. The latter formed sludge, columns, adhesion of erythrocytes to the epithelial lining of the intima and transversely arranged fibrin threads were often noted. The venous blood vessels of the myocardium had uneven lumens. Their endotheliocytes were swollen, and in some places they underwent desquamation in the lumen of the veins. The tunica media and tunica adventitia of veins are represented mainly by collagen fibers, the number of smooth myocytes is low. In the lumens of these vessels, the presence of hemorrhagic, serous content, single formal elements of blood were observed. As a whole, the venous system of the myocardium during acute intoxication with Vipera berus berus venom was characterized by signs of stasis. The defining features of the structural organization of the myocardium were zones of massive hemorrhages, in some places the hemorrhages were of a diffuse character with impregnation of the heart muscle tissue. Erythrocytes often

went beyond blood vessels and were located in interfibrillar spaces (Fig. 3).

Conductive cardiomyocytes (Purkinje fiber cells) were localized between the components of the contractile system of the heart. They stained less intensively than contractile cardiomyocytes, were wider, shorter, sometimes had the appearance of light cords or disordered structures with a small number of myofibrils. The majority of Purkinje cells were characterized by lightening of the cytoplasm due to their pronounced hydropic dystrophy. The latter fact explained the difficult recognition of their nuclei. The nuclei of conducting cardiomyocytes were located in the center of the cells, had signs of heterochromia, and the nuclear-cytoplasmic index was low. In individual cells, the nuclei shifted to the periphery (see Fig. 3).

In the endocardium of animals of the experimental group, swelling of endotheliocytes was detected. The nuclei of these cells were hyperchromic. Areas of detachment of the endothelial lining from the subendothelial layer were observed. In the subendothelial layer, the connective tissue elements increased in volume. In the outer connective tissue layer of the endocardium, the activity of fibroblasts increased and the growth of collagen fibers took place, just as in the previously mentioned layers of the heart.

Discussion

Cardiotoxicity and pronounced electrocardiographic changes are frequent complications of snake bites [16, 18, 24]. The most common are sinus arrhythmia, atrioventricular block and sinus bradycardia. Cases of bites by snakes of the Viperidae family are often associated with such pathologies as myocardial infarction and ischemic stroke, resulting from activation blood coagulation cascade and direct cardiotoxicity of venom proteolytic enzymes, in particular SVMPs. Also, the components of their toxins cause the development of hypofibrinogenemia, damage of the endothelium of vessels and impaired platelet aggregation [17, 25, 26].

According to the literature, the basis of the pathogenesis of myocardial infarction due to bites of snakes of the Viperidae family is also a violation of oxygen supply to cardiomyocytes due to excessive hemolysis of erythrocytes, vasoconstriction of coronary vessels due to significant production of endothelin and the influence of venom safatoxins. Scientists note that the development of myocarditis with pronounced necrosis of contractile myocytes, hemorrhages and accumulation of blood clots in the vessels of the microcirculatory channel of the heart muscle is possible [6, 15, 23].

L. O. Simoes and co-authors [22] studied the effect of Crotalus durissus cascavella venom on the cardiovascular system of rats. In the course of the experiment, it was found that the introduction of the venom of these snakes to animals leads to the development of morphological changes in the heart tissue. Light microscopy established the presence of inflammation and hemorrhages and a decrease in the volume of cells, eosinophilic infiltration, loss of transverse striation of myofibrils, changes in the nuclei of cardiomyocytes, accumulation of granules in the sarcoplasmic reticulum, violation of the integrity of muscle fibers. The venom has also been shown to exert a pronounced inotropic effect by activating NO/cGMP/protein kinase G, leading to hypotension and bradycardia in vivo. NO reduces the flow of Ca2+ ions through L-type channels in rat myocardium. In addition, it increases the activity of cGMP / protein kinase G-dependent phosphorylation of cardiac troponin I and the binding of myosin to protein C, causing muscle relaxation and a negative inotropic effect.

S. Karabuva and co-authors [13, 14] established that the venom of Vipera ammodytes, as well as related European vipers, can have a cardiotoxic effect. The main component that determines the pattern of heart damage is an analogue of secretory PLA2 - amodytilin L. In the isolated perfused heart of rats, it induced pronounced and irreversible conduction disturbances, namely severe atrioventricular blocks. The process was accompanied by an increase in CPK, LDH, AST, troponin I in the blood of the animals, which indicated damage of the heart tissue.

Conclusions

1. Under the conditions of acute intoxication with Vipera berus berus venom in experimental rats, microscopic examination of heart tissue revealed pathological shifts in the structural organization of all layers of the organ. In the epicardium, an increase in the volume of collagen fibers and thickening of vessel walls were characteristic.

2. The most pronounced histological changes were observed in the myocardium. Swelling, disorganization of muscle fibers, their fragmentation, lysis, destruction, loss of characteristic transverse striations, necrosis were detected in it. In addition, an increase in the number of fibroblasts, their activation and, as a result, the growth of connective tissue components, including collagen fibers, in the myocardial tissue were revealed.

3. The endocardium of experimental rats was distinguished by desquamation of the endothelial lining and an increase in the number of active fibroblasts in the outer connective tissue layer.

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СТРУКТУРНІ ЗМІНИ В ТКАНИНІ СЕРЦЯ ЩУРІВ ЗА УМОВ ГОСТРОЇ ІНТОКСИКАЦІЇ ОТРУТОЮ ГАДЮК VIPERA BERUS BERUS

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Серед усіх отруйних тварин змії привертають особливу увагу людства. Випадки отруєнь їх токсинами є надзвичайно поширеними та належать до невирішених проблем охорони здоров'я в усьому світі. Встановлено, що серед цілого ряду ускладнень внаслідок зміїних укусів важливу роль відіграють порушення нормального функціонування органів серцево-судинної системи. Метою дослідження є вивчення особливостей гістологічних змін тканини серця щурів за умов гострої інтоксикації отрутою гадюк Vipera berus berus. Експериментальні дослідження проводили на білих нелінійних щурах самцях. Тварин умовно розподіляли на дві групи - контрольну і дослідну по 10 особин в кожній. Дослідним щурам внутрішньоочеревинно вводили напівлетальну дозу (LD50) (1,576 мг/г$^{-1}$) отрути Vipera berus berus на фізіологічному розчині. Тваринам контрольної

групи внутрішньоочеревинно вводили лише фізіологічний розчин. Виводили щурів з експерименту через 24 години після впливу отрути, знеживлюючи шляхом цервікальної дислокації. Для мікроскопічного дослідження забирали зразки серця. Фіксація матеріалу та приготування парафінових блоків проводили за загальноприйнятими методиками. Забарвлення гістологічних препаратів серця здійснювали Picro Sirius Red/Fast Green. Гістологічні препарати вивчали за допомогою світлового мікроскопа SEO SCAN. Таким чином, за умов гострої інтоксикації отрутою гадюк Vipera berus berus в експериментальних щурів при мікроскопічному дослідженні тканини серця виявлено патологічні зрушення структурної організації всіх шарів органу. В епікарді характерним було збільшення об'єму колагенових волокон, потовщення стінок судин. Найбільш виражені гістологічні зміни спостерігали в міокарді. В ньому відмічали набряк, дезорганізації м'язових волокон, їх фрагментацію, лізис, деструкцію, втрату характерної поперечної посмугованості, некроз. Крім того, виявлено зростання чисельності фібробластів, їх активацію та, як результат, розростання в тканині міокарда компонентів сполучної тканини, в тому числі колагенових волокон. Ендокард дослідних щурів відрізнявся десквамацією ендотеліального вистилення та збільшенням кількості активних фібробластів в зовнішньому сполучнотканинному шарі.

Ключові слова: *гадюки, отрута, серце, фібробласти, деструкція, щури.*