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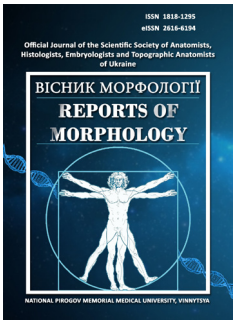

Differences in the structural organisation of liver tissue in experimental rats 1 and 3 hours after administration of Leiurus macroctenus scorpion venom

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Scorpion bites are a serious threat to human health and life in almost all countries of the world. The amount and toxicity of the poison that enters the body of the victims depend on the interspecific variability of these animals. Scorpion venom usually causes the development of local, cardiotoxic, neurotoxic and vegetative effects. The study aimed to determine the differences in the structural organisation of the liver tissue of experimental rats 1 and 3 hours after the administration of the venom of the scorpion Leiurus macroctenus. The study was conducted on 10 male rats (200±10 g), which were injected intramuscularly with 0.5 ml of a solution of venom (28.8 μg/ml; LD_{50}=0.08 mg/kg) of the scorpion Leiurus macroctenus, dissolved in saline (0.9 %). The control group (10 rats) was injected with only 0.5 ml of saline (0.9 %). For microscopic examination, samples of liver tissue from animals of all groups were taken. The pieces were fixed in 10 % formalin solution for 1 day. Then, the pieces were dehydrated in alcohols of increasing concentration and embedded in paraffin blocks. Histological preparations of rat livers were stained with hematoxylin and eosin. Histological preparations were studied using a SEO SCAN light microscope and photodocumented using a Vision CCD Camera video camera with an image output system from histological preparations. One hour after the rats were administered the venom of the scorpion Leiurus macroctenus, no pronounced changes in the structural organisation of the liver of experimental rats were observed. Infiltration of the portal tracts and sometimes the surrounding parenchyma of the organ with lymphocytes, histiocytes and neutrophilic leukocytes was noted. Hepatocytes near the foci of infiltration underwent vacuolar dystrophy, which are reactive changes in response to the action of the venom. In rats that were withdrawn from the experiment three hours after the administration of the venom of the scorpion Leiurus macroctenus, more pronounced changes in the structural organisation of the liver were observed. Areas of disruption of the order of the hepatic lamellae were noted, and the number of binucleated hepatocytes increased, as well as their nuclear-cytoplasmic index. An increase in the number of Kupffer cells was detected; the presence of vacuolar or fatty dystrophy characterised the vast majority of hepatocytes. Pronounced infiltration of the portal tracts and the surrounding liver parenchyma was observed with a predominance of lymphocytes and macrophages.

Keywords: *scorpions, liver, inflammation, macrophages, lymphocytes.*

Introduction

Scorpion stings are a serious threat to human health and life in almost all countries of the world. The amount and toxicity of the venom that enters the body of the victims depend on the interspecific variability of these animals. Scorpion venom usually causes the development of local, cardiotoxic, neurotoxic and vegetative effects. Depending on the predominance of one or another component in the venom, a wide range of clinical signs and symptoms can be observed from local reactions (hyperemia, pain, oedema) to serious consequences, including respiratory, gastrointestinal, cardiovascular or neurological complications [7, 12, 15]. The severity of poisoning depends on the size and type of

scorpion, the amount of venom injected, the body weight of the victim, and the victim's sensitivity to the venom. Studies in recent decades have reported damage to the kidneys, liver, pancreas, heart, and hemolytic disorders as a result of poisoning with toxins from some scorpion species [8, 11].

The evolution of scorpions is approximately 400 million years, during which they have spread throughout the world. To date, more than 2,700 extant species of these animals, numbering about 20 families, have been registered. The extraordinary resistance, adaptability to changing climate conditions, and high survival rate of scorpions have contributed to their colonisation in tropical, subtropical, and temperate regions of almost all continents, except Antarctica and several Pacific islands [1, 14, 30]. However, in recent years, the expansion of human civilisation and the growth of the human population have led to a sharp reduction in the usual habitats of scorpions, but have significantly increased the frequency of poisonings due to their bites.

The liver is one of the essential organs that provide the body's immune defence with a high density of myeloid (such as Kupffer cells, neutrophils or macrophages) and lymphoid (such as natural killer cells, T cells or B cells) immune cells. The human liver contains about 1010 resident lymphocytes, including B cells, T cells and natural killer (NK) cells. Lymphocyte migration increases in response to the activation of inflammatory processes, and intrahepatic compartmentalisation of lymphocytes determines the morphological variant of organ damage [9, 23, 27]. Toxic liver damage due to exposure to poisons, including those of animal origin, is often associated with lymphocytic infiltration, and the nature and degree of inflammation determine the rate of progression and severity of damage. The mechanisms by which toxic compounds activate immune-mediated pathways of liver damage are still being actively studied; however, liver infiltration by effector lymphocytes is a common phenomenon, leading to the destruction of hepatocytes and cholangiocytes and a persistent shift in the structural and functional characteristics of the organ [2, 19, 27].

The study aims to determine the differences in the structural organisation of the liver tissue of experimental rats 1 and 3 hours after the administration of Leiurus macroctenus scorpion venom.

Materials and methods

The study used ten white male laboratory rats weighing approximately 200±10 g (10 – control group was injected with only 0.5 ml of 0.9 % saline; 10 – experimental group), which were housed in the vivarium of the Educational and Scientific Centre "Institute of Biology and Medicine" of Taras Shevchenko National University of Kyiv. The rats were maintained on a standard diet in an accredited vivarium, following the "Standard Rules for the Arrangement, Equipment and Maintenance of Experimental Biological Clinics (Vivaria)". The experiments were conducted in accordance with the current regulatory standards governing research with laboratory animals and in accordance with the principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" [16]. In addition, all procedures with animals complied with the legislation of Ukraine, in particular the Law No. 3447-IV of February 21, 2006 "On the Protection of Animals from Cruelty and Ethical Norms and Rules for Working with Laboratory Animals", which was approved by the Bioethics Committee of the O. O. Bogomolets National Medical University (protocol No. 191 of 01/27/2025).

The rats used in the experiment were divided into two groups: experimental group 1 (5 rats) – histological material was collected 1 hour after the introduction of the poison; and experimental group 2 (5 rats), in which the liver tissues were collected three hours after exposure to the poison. The venom of a scorpion from the Buthidae family, genus Leiurus, species Leiurus macroctenus, was administered to rats once intramuscularly (0.5 ml of venom solution previously dissolved in saline; 28.8 μg/ml; LD_{50}=0.08 mg/kg) [16, 17]. Rats were euthanised by carbon dioxide inhalation, and the liver was immediately removed at 4 °C.

Liver tissue samples from animals of all groups were taken for microscopic examination. The pieces were fixed in 10 % formalin solution for 1 day. Then the pieces were dehydrated in alcohols of increasing concentration and embedded in paraffin blocks. Histological preparations of rat livers were stained with hematoxylin and eosin. Histological preparations were studied using a SEO SCAN light microscope and photographed using a Vision CCD Camera with an image output system from histological preparations [18].

Results

Microscopic studies one hour after administration of Leiurus macroctenus scorpion venom to rats demonstrated the appearance of minor shifts in the normal histoarchitectonics of the animal liver. Hepatocytes were predominantly hexagonal in shape and contained one nucleus, but the presence of binucleate cells was noted. The cytoplasm of hepatocytes was oxyphilic and contained numerous inclusions. Their nuclei had 1-2 nucleoli, and the chromatin occupied a marginal position under the nuclear envelope. Hepatocytes formed hepatic plates that were ordered and located radially from the central vein (Fig. 1).

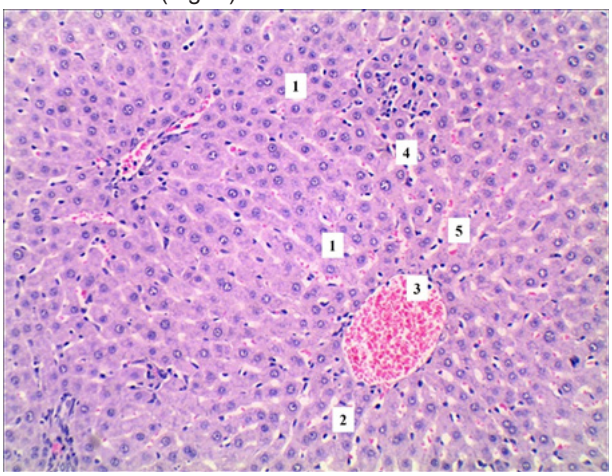

Fig. 1. Microscopic organisation of the liver of an experimental rat 1 hour after administration of the venom of the scorpion Leiurus macroctenus. Hepatocytes (1), hepatic laminae (2), lumen of the central vein (3), space of Disse (4), lumen of the sinusoidal capillary (5). Staining with hematoxylin and eosin. ×100.

Sinusoidal capillaries between hepatic beams were somewhat dilated, and their lumen was mainly filled with erythrocytes. Endothelial lining of capillaries – without signs of desquamation from the basement membrane. Their endothelial cells are somewhat flattened and contain fenestrae in the cytoplasm. The presence of perisinusoidal Kupffer cells in the space of Disse was observed, which had an irregular shape and were distinguished by the presence of processes. They were characterised by elongated hyperchromic nuclei and weakly oxyphilic cytoplasm with numerous inclusions and a well-developed Golgi complex (see Fig. 1, Fig. 2).

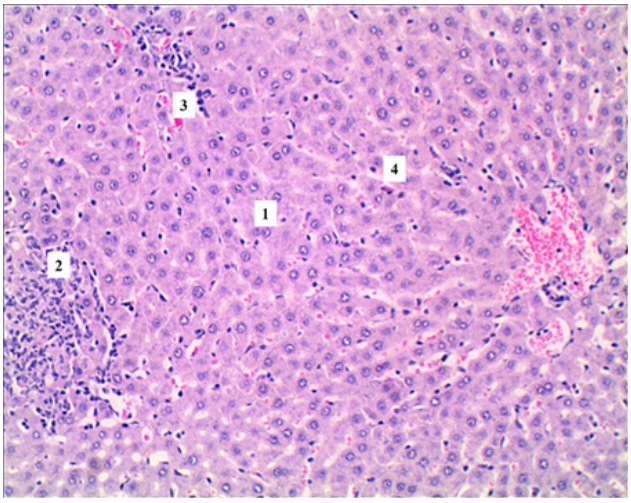

Fig. 2. Histological structure of the liver of an experimental rat 1 hour after administration of the venom of the scorpion Leiurus macroctenus. Hepatocytes (1), lymphohistiocytic infiltration (2), lumen of the sinusoidal capillary (3), space of Disse (4). Staining with hematoxylin and eosin. ×100.

The lumen of the central vein in most histological specimens is dilated. The endothelial cells of the inner lining of the vascular wall are elongated, and their nuclei are hyperchromic. Stasis of formed blood elements, mainly erythrocytes, was noted in the lumen of the central vein (see Fig. 1).

A characteristic feature of the structural organisation of the liver one hour after the start of the experimental study was pronounced histiocytic and lymphocytic infiltration of the portal tracts, sometimes with the presence of neutrophilic leukocytes. Accumulations of lymphocytes were detected around the portal vein and bile ducts. However, partial infiltration of the surrounding parenchyma was also observed in some fields of view. It should be noted that in these areas, individual hepatocytes had signs of vacuolar dystrophy. These structural changes can be regarded as initial reactive changes in response to the action of scorpion venom toxins. The walls of the bile ducts under these conditions did not undergo pronounced changes. They were lined with one row of cubic cells. Their nuclei occupied a central position and contained one nucleolus. Chromatin had a marginal location, formed clumps or was diffusely scattered. The hepatic artery was distinguished by the presence of elongated endothelial cells of the inner membrane with round or oval hyperchromic nuclei. Some endothelial cells protruded into the lumen of the vessel in the form of palisades. The lumen of the hepatic vein was dilated, sometimes with erythrocyte stasis (Fig. 3).

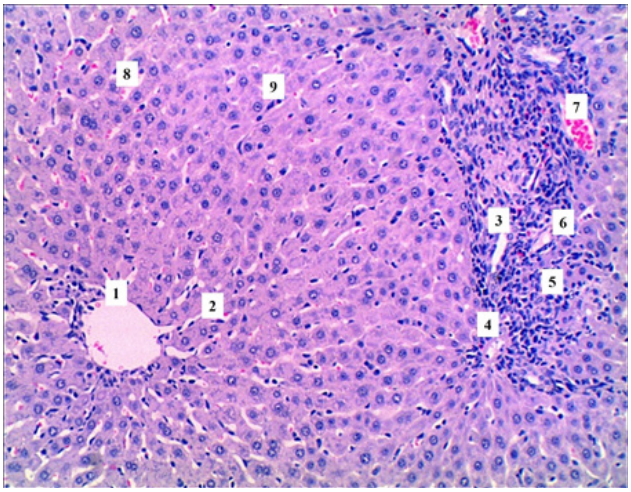

Fig. 3. Morphological organisation of the liver of an experimental rat 1 hour after administration of the venom of the scorpion Leiurus macroctenus. Central vein lumen (1), hepatic lamellae (2), bile duct lumen (3), hepatic artery (4), lymphohistiocytic infiltration (5), portal vein (6), hepatic vein (7), sinusoidal capillary lumen (8), Disse's space (9). Hematoxylin and eosin staining. ×100.

Histological studies of the liver tissue of experimental rats three hours after the start of the experiment and the administration of the scorpion venom Leiurus macroctenus demonstrated the presence of more pronounced changes in the morphological structure of the organ. Hepatocytes formed hepatic plates, which were located mainly radially from the central vein; however, in some fields of view, disturbances in the order of liver cells were noted. The latter had a polygonal shape; their cytoplasm was eosinophilic with numerous signs of vacuolar and fatty dystrophy. The nuclei of hepatocytes were rounded, hyperchromic, and contained 1-2 nucleoli. In the vast majority of hepatocyte nuclei, heterochromatin prevailed, which accumulated under the karyolemma. The karyoplasm was clear and oedematous. Compared with the previous study group, the number of binucleated cells increased, and the nuclear-cytoplasmic index of hepatocytes also increased (Fig. 4).

The lumens of the sinusoidal capillaries of the liver were significantly dilated. Endotheliocytes were characterised by an elongated shape, weakly eosinophilic cytoplasm, and hyperchromic nuclei. In the lumens of the sinusoidal capillaries, accumulations of formed blood elements were observed, in particular erythrocytes and occasionally lymphocytes. In the spaces of Disse between the walls of the sinusoidal hemocapillaries of the liver and hepatocytes, accumulations of Kupffer cells were detected. Their number also increased compared to the study group one hour after the administration of the poison. They had an elongated or close to oval shape, clear cytoplasm, and hyperchromic

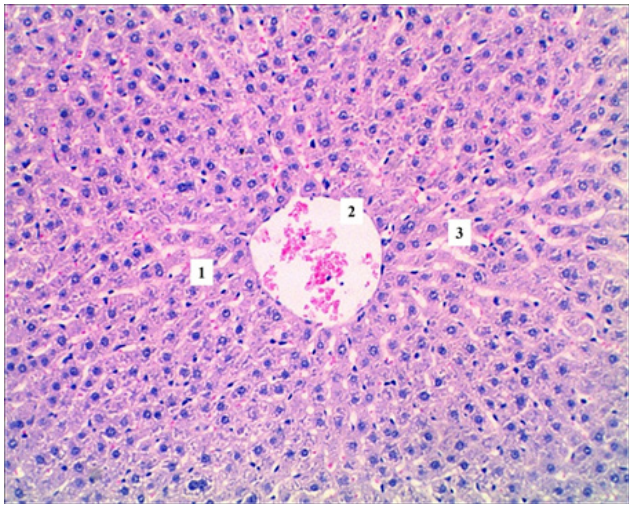

Fig. 4. Histological structure of the liver of an experimental rat 3 hours after administration of the venom of the scorpion Leiurus macroctenus. Liver lamellae (1), lumen of the central vein (2), lumen of the sinusoidal capillary (3). Staining with hematoxylin and eosin. ×100.

nuclei. The presence of an insignificant number of fibroblasts in the intercellular connective tissue, which was somewhat edematous, was also noted (Fig. 5).

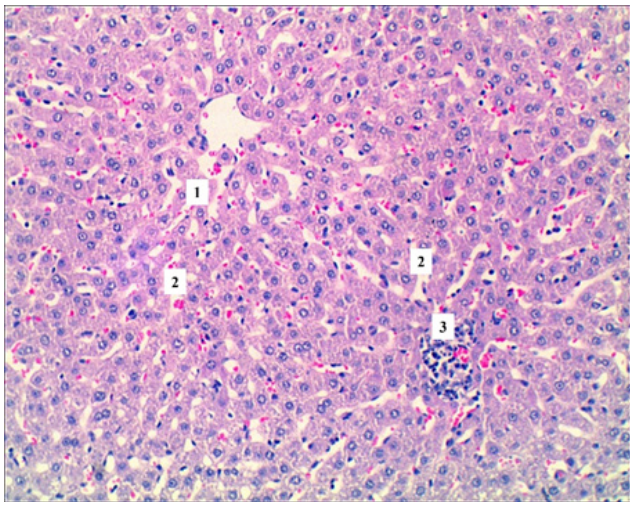

Fig. 5. Microscopic changes in the liver of an experimental rat 3 hours after administration of the venom of the scorpion Leiurus macroctenus. Hepatocytes (1), lumens of sinusoidal capillaries (2), inflammatory infiltrate (3). Staining with hematoxylin and eosin. ×100.

The lumens of the central veins were significantly dilated and markedly full of blood, contained clusters of erythrocytes, and their adhesion to the vein wall was also noted. The endothelial cells of the inner membrane of the central vein had a flattened shape, oxyphilic cytoplasm, and markedly hyperchromic nuclei. Individual endothelial cells in the form of palisades were directed into the lumen of the vein. Moderately pronounced lymphocytic infiltration was observed around the central vein (Fig. 6).

The portal tracts were characterised by significant lymphocytic infiltration. The lumens of the bile ducts were

Fig. 6. Microscopic organisation of the liver of an experimental rat 3 hours after administration of the venom of the scorpion Leiurus macroctenus. Hepatic lamellae (1), hepatocytes (2), lumen of the central vein (3), portal tract (4), interlobular bile duct (5), interlobular artery (6), lumen of the sinusoidal capillary (7). Staining with hematoxylin and eosin. ×100.

dilated, and their wall was represented by one row of cubic cells with an increased nuclear-cytoplasmic index. The cytoplasm of these cells was weakly oxyphilic, the nuclei contained one nucleolus, had a clear karyoplasm, and the chromatin occupied a marginal position. The walls of the interlobular bile ducts were slightly thickened. Thickened, edematous walls also distinguished the interlobular arteries. Their epithelial lining was sometimes incomplete, and areas of desquamation of the endothelium from the basement membrane were detected. The muscular coat of the arteries had signs of oedema and was represented mainly by smooth muscle cells with homogeneous eosinophilic cytoplasm and elongated hyperchromic nuclei. The lumens of the interlobular veins were often narrowed due to infiltration and contained formed blood elements (Fig. 7).

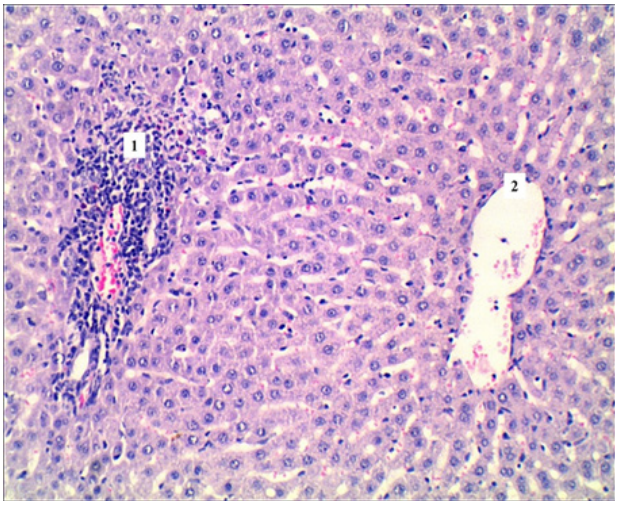

Fig. 7. Histological changes in the liver of an experimental rat 3 hours after administration of the venom of the scorpion Leiurus macroctenus. Inflammatory infiltrate (1), lumen of the central vein (2). Staining with hematoxylin and eosin. ×100.

A distinctive feature of this study group was the formation of foci of pronounced lymphocytic infiltration, but not only in the areas of the portal tracts. These infiltrates were represented by lymphocytes, macrophages and to a lesser extent, plasma cells and segmented neutrophils. In the areas of infiltration, narrowing of the lumens of the sinusoidal hemocapillaries of the liver, a significant degree of vacuolar dystrophy of hepatocytes, and their apoptosis were detected. The appearance of karyolysis and karyopyknosis of the nuclei distinguished individual hepatocytes. A denser arrangement of hepatocytes was observed around the inflammatory infiltrates.

Discussion

Thus, one hour after the administration of the venom of the scorpion Leiurus macroctenus to rats, infiltration of the portal tracts and the organ parenchyma with various types of leukocytes was noted. Hepatocytes near the foci of infiltration underwent vacuolar dystrophy. In rats that were withdrawn from the experiment three hours after the administration of the venom, areas of disruption of the order of the hepatic lamellae were noted, an increase in the number of Kupffer cells was detected, and the presence of vacuolar or fatty dystrophy characterised the majority of hepatocytes. H. A. Fetaih et al. [13] studied histopathological changes in the structure of the liver under the influence of the venom of the scorpion Androctonus amoreuxi in experiments on mice. 6 hours after the administration of ¼ LD_{50}, significant blood stasis was detected in the vessels of the organ. On the 4th day, hydropic degeneration of hepatocytes, karyolysis and karyorrhexis of nuclei were noted. An increase in the concentration of the poison, namely ½ LD_{50}, after 9 hours of observation showed the appearance of extramedullary hematopoiesis islands in the liver and dilation of sinusoidal capillaries. Already on the 4th day of the study, at the indicated dose of poison, dilation of blood vessels, fibrinoid degeneration, and deposition of weakly basophilic homogeneous material in the portal zones of the organ were detected.

The bites of scorpions, Leurus quinquestriatus, have been proven to cause changes in the morphological organisation of the rat liver. Histological examination of the organ after injection of the poison to animals at a dose of 0.03 mg/kg revealed pronounced oedema of hepatocytes, which led to a change in the shape of the cells and the “disappearance” of most sinusoidal capillaries. The cytoplasm of hepatocytes underwent vacuolization and the appearance of areas that were not stained with hematoxylin and eosin. Hypochromia of the nuclei and their pyknotic changes were noted. Degenerative changes of individual nuclei and chromatin margination were also observed. In some fields of view, hepatocyte necrosis and congestion in the portal vein branch were present [5, 26].

Studies by Khemili D. [20] showed that the venom of scorpions Androctonus australis hector at a dose of 0.5 mg/kg caused the development of pronounced pathological changes in the liver parenchyma, including necrosis of hepatocytes, destruction of hepatic architectonics and massive immigration of inflammatory cells into the sinusoids.

Clinical observations of patients after scorpion bites and experimental studies demonstrate cases of toxic hepatitis and coagulopathy. In biochemical studies under these conditions, an increase in ALT, AST, LDH, and, rarely, hyperbilirubinemia is recorded. The mechanisms of involvement of liver damage caused by scorpion bites remain unclear, although the hypothesis of direct hemolytic and cytotoxic effects of the venom prevails. In addition, stimulation of neurotransmitters, catecholamines and the release of cytokines and inflammatory mediators are usually associated with hepatotoxicity and haematological disorders. In addition, intravascular hemolysis, coagulopathy, and thrombocytopenia are characteristic, which may act as indirect factors of liver damage [3, 6, 22]. The development of oxidative stress almost always characterises liver damage due to factors of various origins. Recent studies have demonstrated that there are specific patterns of protein expression in the liver that are induced in mammalian cells in response to hydroperoxide stress. This modulation occurs due to the activation of redox transcription factors, such as Egr-1, NF-kappaB, and AP-1, as well as G proteins [21]. Cellular kinases, especially the mitogen-activated protein kinase family, also play an essential role. Protein expression disorders emphasise the importance of signalling pathways dependent on the balance of redox processes. Excessive production of ROS exposes the liver to oxidative stress and leads to hepatocyte apoptosis [4, 10]. Currently, the study of cellular mechanisms that protect against oxidative stress is highly relevant. Despite the minimal amount of data, only a few specific genes are known that are crucial for the control of cellular function in cases of oxidative liver damage. Apurinic/apyrimidinic endonuclease (APE)/redox factor (Ref)-1 is a prime example of this mechanism. The APE/Ref1 enzyme is a key driver of excision repair, which exhibits properties of repair and redox control.

Activation of inflammatory processes and oxidative stress underlie the pathogenesis of organ damage caused by scorpion venom. However, the relationship between them is not fully understood. Toll-like receptors play a crucial role in stimulating the inflammatory response, and evidence is accumulating that TLRs, in particular TLR4, may be involved in both redox imbalance and inflammation induction. Recent studies have demonstrated that blocking TLR4 attenuates the inflammatory response mediated by neutrophils, as evidenced by a decrease in the number of these cells in the blood, as well as inhibition of their degranulation and sequestration in lung, liver, and kidney tissues [29]. In addition, TAK-242 (a small-molecule inhibitor of Toll-like receptors) caused a significant decrease in the content of nitrites, malondialdehyde and carbonyl groups of proteins, associated with an improvement in the functioning of the antioxidant defence system in all organs studied, except the heart [20]. It has been proven that the TLR family of receptors is involved in warning the immune system about the possible negative impact of factors of various origins, and

the receptors themselves can be activated by DAMPs, which are released under the influence of stress factors, including scorpion stings, as previously noted [24, 30].

Conclusions

1. One hour after the administration of Leiurus macroctenus scorpion venom to rats, no pronounced changes in the structural organisation of the liver of experimental rats were observed. Infiltration of the portal tracts and sometimes the surrounding parenchyma of the organ with lymphocytes, histiocytes and neutrophil leukocytes was noted. Hepatocytes near the foci of infiltration underwent vacuolar dystrophy, which are reactive changes in response to the action of the venom.

2. In rats that were removed from the experiment three hours after the administration of Leiurus macroctenus scorpion venom, more pronounced changes in the structural organisation of the liver were observed. Areas of disruption of the order of the hepatic lamellae were noted, and the number of binucleated hepatocytes increased, as well as their nuclear-cytoplasmic index. An increase in the number of Kupffer cells was detected; the presence of vacuolar or fatty dystrophy characterised the vast majority of hepatocytes. Pronounced infiltration of the portal tracts and surrounding liver parenchyma with a predominance of lymphocytes and macrophages was observed.

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ВІДМІННОСТІ СТРУКТУРНОЇ ОРГАНІЗАЦІЇ ТКАНИНИ ПЕЧІНКИ У ЕКСПЕРИМЕНТАЛЬНИХ ЩУРІВ ЧЕРЕЗ 1 ТА 3 ГОДИНИ ПІСЛЯ ВВЕДЕННЯ ОТРУТИ СКОРПІОНА LEIURUS MACROCTENUS

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Укуси скорпіонів є серйозною загрозою для здоров’я та життя людей майже в усіх країнах світу. Кількість і токсичність отрути, яка потрапляє до організму постраждалих залежить від міжвидової мінливості цих тварин. Отрута скорпіона зазвичай спричиняє розвиток місцевих, кардіотоксичних, нейротоксичних і вегетативних ефектів. Мета дослідження – визначити відмінності структурної організації тканини печінки експериментальних щурів через 1 та 3 години після введення отрути скорпіонів Leiurus macroctenus. Дослідження проводили на 10 щурах-самцях щурів (200±10 г), яким внутрішньом’язово вводили 0,5 мл розчину отрути (28,8 мкг/мл; LD50=0,08 мг/кг) скорпіона Leiurus macroctenus, розчиненого у фізіологічному розчині (0,9 %). Контрольній групі (10 щурів) вводили лише 0,5 мл фізіологічного розчину (0,9 %). Для мікроскопічного дослідження вилучали зразки тканини печінки тварин всіх груп. Шматочки фіксували в 10 % розчині формаліну протягом 1 доби. Далі проводили дегідратацію шматочків в спиртах зростаючої концентрації та заливали в парафінові блоки. Забарвлення гістологічних препаратів печінки щурів здійснювали гематоксиліном та еозином. Гістологічні препарати вивчали за допомогою світлового мікроскопа SEO SCAN та фотодокументували за допомогою відеокамери Vision CCD Camera з системою виводу зображення з гістологічних препаратів. Через одну годину після введення щурам отрути скорпіонів Leiurus macroctenus не спостерігали виражених зрушень структурної організації печінки експериментальних щурів. Відмічали інфільтрацію портальних трактів та подекуди оточуючої паренхіми органу лімфоцитами, гістіоцитами та нейтрофільними лейкоцитами. Гепатоцити поблизу вогнищ інфільтрації зазнавали вакуольної дистрофії, що є реактивними змінами у відповідь на дію отрути. У щурів, яких виводили з експерименту через три години після введення отрути скорпіонів Leiurus macroctenus спостерігали більш виражені зміни структурної організації печінки. Відмічали ділянки порушення впорядкованості печінкових пластинок, збільшувались чисельність двоядерних гепатоцитів, а також їх ядерно-цитоплазматичний індекс. Виявляли зростання кількості клітин Купфера, переважна більшість гепатоцитів характеризувалась наявністю вакуольної чи жирової дистрофії. Спостерігали виражену інфільтрацію портальних трактів та оточуючої паренхіми печінки з переважанням лімфоцитів і макрофагів.

Ключові слова: *скорпіони, печінка, запалення, макрофаги, лімфоцити.*

Author’s contribution

Haidai O. S. – conceptualization, research, writing of the original draft.
Dzevulska I. V. – methodology, formal analysis.
Samborska I. A. – project administration, resources.
Shvager O. V. – validation, software.