REVIEW ARTICLE

CONTENTS

General structure of scorpion venom and its influence on morphological parameters of the mammalian liver

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ABSTRACT

Aim: To determine the general patterns of the structure of scorpion venom and its influence on the morphological parameters of the mammalian liver.

Materials and Methods: A thorough literature analysis was conducted on the basis of PubMed, Google Scholar, Web of Science, and Scopus databases. When searching for information of the general patterns of the structure of scorpion venom and its influence on the morphological parameters of the mammalian liver, we used the following combinations of keywords: "scorpions", "toxins", "liver", "hepatotoxicity", "hepatocytes". When processing the search results, we chose the newest publications up to 5 years old or the most thorough publications that vividly described the essence of our topic. After conducting a detailed review of the abstracts of the articles and getting acquainted with their full content, 32 sources were selected that fully corresponded to the results of the request.

Conclusions: Scorpion venom causes the development of local, cardiotoxic, neurotoxic effects and effects of autonomic nervous system. Depending on the predominance of a particular component in the venom, a wide range of clinical signs and symptoms can be observed from local reactions (hyperemia, pain, edema) to serious consequences, including respiratory, gastrointestinal, cardiac or neurological complications. The influence of toxic components on the structural and functional parameters of the mammalian liver is currently at the stage of comprehensive and thorough study. It has been established that under the conditions of administration of scorpion venom to experimental animals, hydropic degeneration and karyorrhexis of hepatocytes, fibrinoid necrosis, blood stasis in the vessels, an increase in the level of enzymes - ALT, AST, LDH were noted.

KEYWORDS: liver, hepatotoxicity, toxins, hepatocytes, scorpion

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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 depends on the interspecific variability of these animals. Scorpion venom usually causes the development of local, cardiotoxic, neurotoxic and effects of autonomic nervous system. Depending on the predominance of a particular component in the venom, a wide range of clinical signs and symptoms can be observed from local reactions (hyperemia, pain, edema) to serious consequences, including respiratory, gastrointestinal, cardiac or neurological complications. The severity of poisoning depends on the size and type of scorpion, the amount of venom injected, as well as the body weight of the victim and sensitivity to the venom. Studies in recent decades have reported damage of the kidneys, liver, pancreas, heart, as well as the appearance of hemolytic disorders as a result of poisoning with toxins of some species of scorpions [1, 2].

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 have been recorded, numbering about 20 families. The extraordinary resilience, adaptability to changing climate conditions and high survival rates of scorpions have contributed to their colonization in tropical, subtropical and regions of almost all continents, except Antarctica and several Pacific islands. However, in recent years, the expansion of human civilization 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. In several regions of the world, including Central America, southern Latin America, Western Asia, North Africa and the Middle East, scorpionism has become an important health problem [3]. More than 1.2 million cases of scorpion stings are reported worldwide each year, with consequences ranging from localized pain or inflammation to serious clinical complications

or death, depending mainly on the types and amounts of neurotoxins present in the scorpion venom. In particular, most species of scorpions in the Buthidae family are more venomous than those in the Scorpionidae and Hemiscorpiidae families. A scorpion sting usually causes local pain that lasts for a few minutes. Meanwhile, the neurotoxins released by venomous scorpions cause sympathetic excitation and the release of catecholamines into the blood plasma, leading to severe clinical manifestations, including high blood pressure, cardiac arrhythmias, pulmonary edema, loss of consciousness, and sometimes death. [4, 5].

AIM

The aim of the study was to determine the general patterns of the structure of scorpion venom and its influence on the morphological parameters of the mammalian liver.

MATERIALS AND METHODS

A thorough literature analysis was conducted on the basis of PubMed, Google Scholar, Web of Science, and Scopus databases. When searching for information of the general patterns of the structure of scorpion venom and its influence on the morphological parameters of the mammalian liver, we used the following combinations of keywords: "scorpions", "toxins", "liver", "hepatotoxicity", "hepatocytes". When processing the search results, we chose the newest publications up to 5 years old or the most thorough publications that vividly described the essence of our topic. After conducting a detailed review of the abstracts of the articles and getting acquainted with their full content, 32 sources were selected that fully corresponded to the results of the request.

ETHICS

All sources used in this literature review are publicly available.

AI STATEMENT

The author states that no AI tools were used in writing this article.

REVIEW AND DISCUSSION

For the purpose of hunting and protection from predators, in the process of long evolution, scorpion venoms have acquired extraordinary molecular diversity, acquiring high activity, specificity, structural variability and a wide range of clinical effects. Among the main non-protein components of scorpion venom, lipids, nucleotides, free amino acids, organic acids, etc. are distinguished. However, the high viability and extraordinary adaptability of scorpion venom are explained precisely by the complex heterogeneous proteins contained in them, including neurotoxins, long-chain cationic antimicrobial peptides, cytolytic peptides, phospholipases, serine proteases, mucoproteins, lysozymes. Among them, short-chain neurotoxic peptides, which constitute 10–70% of the venom content, are the subject of interest to many scientists, since their study is important for assessing the harmful effects on cells and tissues of the victim's body, as well as the potency and selectivity of neurotoxins for certain ion channels. At the same time, progressive achievements in biotechnology have facilitated the identification of a wide range of scorpion venom peptides, some of which have found use in the manufacture of medicines. [6, 7].

According to their structural and functional properties, the peptide components of scorpion venom can be divided into two large groups: disulfide-bridged peptides (DBPs) and non-disulfide-bridged peptides (NDBPs). DBPs usually consist of 13–70 amino acids with three or four disulfide bridges. They include a number of toxins, such as sodium channel toxins (NaTx), potassium channel toxins (KTx), calcium channel toxins (CaTx), chloride channel toxins (CLTx), and TRP channel toxins (TRPTx). These toxins are capable of affecting the permeability of ion channels. NDBPs contain 13–56 amino acids and do not have specific targets among ion channels. However, they have attracted increasing attention in recent years due to their diverse biological and pharmacological effects, such as antimicrobial, antiviral, and antitumor effects. [8].

NaTx are major components of scorpion venom that target voltage-gated Na^+ channels and cause paralysis or death of the victim. They are long-chain venom toxins consisting of 13–56 amino acid residues, most of which contain four disulfide bridges, although some may have three. Structurally, all NaTx share a conserved cysteine-stabilized α-helix and β-sheet (CSαβ) that are cross-linked by 3 or 4 intramolecular disulfide bonds. Depending on the binding site to the ion channel and whether it affects the opening or closing dynamics of Na^+ channels, NaTx can be further divided into α-NaTx and β-NaTx. α-NaTx stimulate inhibition or delay of Na^+ channel inactivation by binding to receptor site 3 (located in domain IV of the ion channel), whereas β-NaTx alters the dynamics of activation of these channels by binding to receptor site 4 (located in domain II of the ion channel). It has been established

that α-NaTx are able to prolong the action potential of excitatory cells and cause paralysis or cardiac arrhythmias, while β-NaTx mainly induce a response in the body of the victims, mediated by monoclonal antibodies or muscle spasms [9, 10].

KTx are among the most common types of scorpion venom neurotoxins that inhibit the activity of potassium ion channels. Due to their unique interaction with K^+ channels, KTx have become indispensable molecular tools for assessing the structural and functional characteristics of various K^+ channels. KTx are typically composed of 23–64 amino acids and contain 2–4 disulfide bridges. Depending on their amino acid sequence, these peptides can be classified into α-KTx, β-KTx, γ-KTx, κ-KTx, δ-KTx, λ-KTx, and ε-KTx [11].

α-KTx is the largest subgroup of KTx, typically includes peptides of 23–43 amino acid residues with 3 or 4 disulfide bridges that share a conserved CSαβ framework. In addition, more than 31 α-KTx subfamilies (α-KTx1 to α-KTx31) have been identified to date, most of which exert their inhibitory activity through interactions between a functional domain located on their β-sheets and amino acid residues surrounding the K1.x pore filters. In contrast to α-KTx, β-KTx (also known as orphan toxins) are approximately 60 amino acid residues longer. α- and β-KTx share a CSαβ framework with three disulfide bridges. β-KTx is mainly found in scorpion species belonging to the genera Androctonus, Mesobuthus, and Tityus. These toxins are characterized by an α-helical N-terminus and a tightly coiled C-terminal region with a CSaβ motif [12, 13]. They exhibit potent antibacterial and hemolytic activity, as well as selective inhibition of potassium channels. γ-KTx contain 3 or 4 disulfide bridges and can selectively block Kv11.x. In contrast to the above three groups of KTx, κ-KTx with two disulfide bridges contain a CSαα framework consisting of two short α-helices connected by a β-sheet; this structural difference results in low-affinity inhibition of potassium channels. δ-KTx constitute a new subcategory of KTx that have Kunitz-type peptides in their structure and exhibit protease and potassium channel inhibition properties. Both λ-KTx with three disulfide bridges and ε-KTx with four disulfide bridges inhibit potassium channels with low affinity, similar to κ-KTx. In vitro experiments have demonstrated that voltage-gated K^+ channels play an important role in immune reactivity. Inhibition of their activity leads to inhibition of T-cell activation and the appearance of delayed-type hypersensitivity. In particular, butanthoxin, which is present in the venoms of three Brazilian scorpions T. serrulatus, T. bahiensis and T. stigmurus, reversibly blocks K^+ channels and inhibits T-cell proliferation and IL-2 production. [14, 15, 16].

Experimental studies of various scorpion families, including Vaejovidae, Euscorpiidae, Hemiscorpidae, Scorpionidae and Buthidae, have identified only a few calcium channel-specific toxins. The CaTx group typically contains 33–36 amino acids with 2–3 disulfide bridges. Most CaTx activate ligand-gated Ca^{2+} channels. A variety of calcins (hemicalcin, gadrocalcin, maurocalcin and opicalcin) have affinity for ryanodine receptors (RyRs), which regulate intracellular Ca^{2+} dynamics from the endoplasmic and sarcoplasmic reticulum. RyRs play an important role in the excitation-contraction processes of the heart and skeletal muscle. Calcins, acting as RyR agonists, regulate elevated intracellular Ca^{2+} levels and induce systolic paralysis. In addition, most calcins are amphiphilic and highly alkaline, which gives them the ability to penetrate inside the cell. [17, 18, 19].

ClTx is a class of peptides that can inhibit the influx of Cl^- ions into the cell membrane. Most members of this group consist of 35–38 amino acids with four disulfide bridges. The classic representative of ClTx is chlorotoxin (CTX), which consists of 36 amino acids and was first isolated from the venom of the giant yellow Israeli scorpion Leiurus quinquestriatus and exhibits a wide range of biological and pharmacological properties. ClTX has been shown to bind to neuroectodermal glioblastoma (GBM) due to its ability to penetrate the blood-brain barrier while showing minimal cross-reactivity with normal brain cells, which plays an important role in the diagnosis and treatment of glioma. [20, 21].

NDBPs are peptides of 13–56 amino acid residues with an extremely heterogeneous composition. In comparison to scorpion venom peptides containing disulfide bridges, NDBPs do not exhibit a conserved or predictable structure-function relationship. Most of these peptides are cationic molecules that exhibit remarkable structural flexibility. In aqueous solutions, these peptides are capable of conformational changes. However, in environments that mimic cell membranes, they readily adopt an amphipathic α-helical structure. This characteristic allows them to interact with a wide range of biological targets, but they do not have any specific molecular targets known to date. [22-24].

The vast majority of scientific sources contain data on the damage of the cardiovascular, respiratory, nervous and excretory systems by scorpion toxins [25-29]. A careful analysis of recent studies has shown a significant limitation of information on histological and biochemical changes in the liver under conditions of poisoning with scorpion toxins.

Fetaih H. A. et al. [30] in experiments on mice studied histopathological changes in the structure of the liver under the influence Androctonus amoreuxi scorpion

venom. 6 hours after the introduction of ¼ LD50, 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 venom, namely ½ LD50, 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 venom, 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 the scorpion Leiurus quinquestriatus have been proven to cause changes in the morphological organization of the rat liver. Histological examination of the organ after injection of the venom in a dose of 0.03 mg/kg revealed marked edema 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 in individual nuclei and chromatin margination were also observed. In some fields of view, hepatocyte necrosis and congestion in the portal vein branch were present. [31].

Clinical observations of patients after scorpion stings demonstrate cases of toxic hepatitis and coagulopathy. Biochemical studies under these conditions record an increase in ALT, AST, LDH, rarely hyperbilirubinemia. The mechanisms of liver damage caused by scorpion stings remain unclear, although the hypothesis of a direct hemolytic and cytotoxic effects of the venom prevails. In addition, stimulation of mediators (neurotransmitters, catecholamines) and the release of cytokines and inflammatory mediators are usually associated with hepatotoxicity and hematological disorders. In addition, intravascular hemolysis, coagulopathy, thrombocytopenia are characteristic, which may act as indirect factors of liver damage. [32].

CONCLUSIONS

Scorpion venom causes the development of local, cardiotoxic, neurotoxic effects and effects of autonomic nervous system. Depending on the predominance of a particular component in the venom, a wide range of clinical signs and symptoms can be observed from local reactions (hyperemia, pain, edema) to serious consequences, including respiratory, gastrointestinal, cardiac or neurological complications. The influence of toxic components on the structural and functional parameters of the mammalian liver is currently at the stage of comprehensive and thorough study. It has been established that under the conditions of administration of scorpion venom to experimental animals, hydropic degeneration and karyorrhexis of hepatocytes, fibrinoid necrosis, blood stasis in the vessels, an increase in the level of enzymes - ALT, AST, LDH were noted.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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