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The Biological Effects of Scorpion Venom: Article review

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Abstract
Scorpion venom can lead to serious medical issues and even death. It comprises a complex of numerous toxins with diverse biological features and activities. The clinical manifestations of envenoming are thought to be caused by neurotoxins, major constituents in scorpion venom. They are extremely selective and powerful ligands for multiple ion channel types. Consequently, they present desirable molecules for the development of innovative medications, including those for the treatment of cardiovascular diseases, cancer, and neurological issues. Notwithstanding the uncertainty and complexity regarding the pathophysiology of envenomation, venom and its accompanying host immunological reactions are known to induce the synthesis of cytokines, critical molecules of inflammation. This review sheds light on scorpion-derived venom and its primary toxins, as well as their biological pathology and the treatment of scorpion stings.

Keywords: scorpion venom, neurotoxins, pathophysiology, envenomation, cytokines.

1. Background

Being members of the Arachnida class and the Scorpiones order, scorpions are considered venomous arthropods. About 1500 species in 18 families of scorpions have been described globally (1). Just about 30 of these species, all Buthidae family members, are dangerous to the human species and can result in serious envenomation or eventually death (2), whereas other Scorpionidae and Hemiscorpiidae species have also been classified as hazardous (3). These clinically important scorpion species are found across North Africa, Asia, the Middle East, as well as India and belong to the following genera Androctonus, Buthus, Mesobuthus, Buthotus, Parabuthus, and Leirus. (4). Anyone, especially children, can get fatally envenomated as a result of incidents involving scorpion stinging, which are exceedingly common in subtropical and tropical regions (5). Globally, there are 1.5 million scorpion envenomings are reported each year, resulting in 2000–3000 fatalities according to national public health statistics (4). Most scorpion venom effects, such as myocardial injury, irregular heartbeats, pulmonary edema, and shock, are triggered by the release of the mediators of the autonomic nervous system (6). Hence, by relying on scorpion species, the symptoms may worsen within a short period of time, causing serious consequences.

The neurotoxins present in scorpion venom frequently cause sweating, nausea, vomiting, hyperactivity, heart failure, arrhythmia, excessive salivation, and coma in more extreme symptoms, and they may even prove lethal in the long run. The neurotoxins of scorpion venom also significantly increase the amount of neurotransmitters released (7). Nonetheless, people have used scorpion body parts and venoms for thousands of years in traditional medicine despite the adverse and occasionally fatal effects of scorpion envenoming. (7). This review, which emphasizes on each of the clinical and experimental studies concerning the consequences of scorpion venom on the human body, attempts to provide a thorough update on scorpion venom research. It is especially important to understand the natural history of envenomation, the risk associated with its lethal forms, the processes associated with dysfunction of organs or body systems that typically happen in severe envenomation, and their potential for recovery

provided that standard treatments typically available in ICUs are provided. Initially, the components of scorpion venom, as well as the clinical signs and symptoms of various stages of scorpionism, are presented. The development of novel options, such as next generation antivenoms, has been explored in conjunction with existing therapies.

2. Scorpion venom molecular content

Scorpions implement their secreted toxins to repel predators and during prey capture. Venom from scorpions has a highly diversified and intricate structure. The overwhelming of study emphasis has, to now, been focused on small scorpion venom peptides, primarily due to their exhibition of wide of pharmacological properties. The venom is comprised of serotonin, mucopolysaccharides, histamine, phospholipase, enzyme inhibitors, and proteins commonly referred to as neurotoxic peptides. (8). Toxins are the components of scorpion venom that have received the greatest attention due to their behavior as neurotoxins through their exerted pharmacological influence on ion channels. For both humans and other animals, poisons that impact sodium channels are the most significant. Such toxins, which are classified as either α-toxins or β-toxins, can delay the closure of voltage-gated Na+ channels or permit their opening at greater negative potentials respectively (9). Potassium, chlorine, and calcium channels are also affected by other known scorpion poisons. Non-disulfide-bridged peptides (NDBPs) are among the substances found in scorpion venom (10). The NDBP group includes a sizeable percentage of scorpion venom (9). Scorpion toxins are divided into several categories based on their composition, mode of toxic action, and their binding receptors on multiple ionic channels or channel subtypes (11). A limited fraction of peptides isolated from the venom of multiple scorpion species make up each class; these peptides were chosen for their bioactive components and consistency with the morphological characteristics of each peptide family. α- and β -toxins are the two primary groups of long-chain toxins known to have an impact on sodium channels. (11). In a membrane-dependent manner, α-toxins bind to the third receptor site of the voltage-gated sodium channels of vertebrate species (12). The findings of multiple studies have shown how toxins affect the body's physiology. As sodium channel receptor affinity is remarkably influenced by the membrane potential, the primary outcome of α-toxins is to extend the action potential of both neurons and muscular tissue (11). American scorpion-derived β-toxins alter the membrane potential to a more negative state by interacting with the fourth receptor site on vertebrate sodium channels (13). A sensor out of four voltage sensors in the Na+ channel is thought to be the sole sensor to which the -scorpion toxin binds (14). In accordance with conventional notions of sodium channel gating, each sodium channel's voltage sensor has a unique mechanism for activation, and at least three of them must exist in an active state for the channel to open. β- toxin activation causes myoclonic or spastic muscle reactions. (15). Chlorine, calcium, and potassium channels are all impacted by other documented scorpion poisonings. Although synergistic activities might cause clinical symptoms, they don't seem to have any significant impact on human envenomation (16, 17).

3. Intermediary Factors In Scorpion Envenomation

Although scorpion envenomation is not contagious, it can cause a systemic inflammatory reaction. An inflammatory reaction is generated by a cascade involving systems, cell components, and mediator release (18). Vertebrates produce antibodies in response to antigen exposure through a few processes involving many cellular interactions. The T-cell antigen receptor first identifies the antigen-presenting cells. Finally, B cells generate antibodies that can detect the initiating antigens with high specificity. T cells produce cytokines and/or engage in cell-cell interactions to assist B cells in producing antibodies in the interim between the two antigen-specific processes. One of the key aspects of this pathophysiology is the secretion and activation of proinflammatory mediators (19). Th1 and Th2, two subpopulations of T cells that differ in how their effectors perform these tasks, release different cytokines in response to antigenic stimulation (20). The three main cytokines under the potent release by cells of Th1 pathway are as follows interleukin-2 (IL-2), interferon (IFN), and tumor necrosis factor (TNF). These cytokines

enhance cell-based immune reaction elicited against penetrating intracellular pathogenic organisms or their toxic products through their contribution to macrophages activation. Furthermore, IgG2a opsonizing antibodies are produced by Th1 cells (20). The Th2 subpopulation produces several cytokines of the interleukin family like IL-4 and IL-6 and is crucial for defense against external parasites by inducing IgE and IgA (20). Excessive production of these mediators can cause shock, organ dysfunction, and death (21). Conversely, cytokines released against inflammation notably IL-5 and IL-10 are vital for lessening the inflammatory response's intensity and establishing homoeostasis needed for an optimal organ function. However, an overactive anti-inflammatory response may dampen the body's immune system (22) The capability of scorpion venom to manufacture cytokine-release stimulatory molecules, notably catecholamines, corticosteroids, bradykinin, and prostaglandins, renders it likely that this venom will excite the neuroendocrine-immunological axis.

Increasing evidence points to an association between morbidity and death in critically sick patients and the surplus of particular cytokines, such as interleukin-6 (23). TNF is a cytokine that has powerful pro-inflammatory effects on metabolic and inflammatory illnesses, including envenomation, which are susceptibility agents of cardiovascular disorders. The principal source of TNF is monocytes and their activated form, macrophages. Throughout the course of envenomation, lymphocytes and macrophages govern a number of inflammatory reactions, which include the release of TNF, which in turn enhances the release of IL-1 and IL-6, the upregulation of adhesion molecules, the growth of fibroblasts, and the onset of cell-associated toxicity and apoptosis (24).

TNF- is a crucial inflammation-reinforcing cytokine as a consequence its of its induction to the synthesis of nitric oxide and other proinflammatory cytokines resulting in a chronic delay of the subsequent hypersensitivity reactions (25). Nitric oxide (NO), a free radical generated by the enzyme NO synthase from its precursor amino acids, the L isoform of both arginine and citrulline, regulates the tone of the vessels and their vasomotor activity for being the major factor derived from the endothelium.The maintenance of vasodilator tone, neurotransmission, and the pressure of the arteries are just a few physiological processes where NO is also believed to serve as a second messenger. Activation of the iNOS has been proposed to cause cytokine-mediated circulatory shock (26).

4. Scorpion toxicity and pathophysiology

Scorpion venoms are extremely poisonous and act quickly, accounting for the early symptoms seen in envenomed individuals. The pathologies caused by envenomation include a wide range of sympathetic and parasympathetic stimulation as well as central symptoms, including heat, irritability, vomiting, excessive tremor, and convulsion. Instances of severe symptoms are typically caused by Centruroides spp infection. (27). Each of the five continents has its own unique pathogenesis for scorpion envenoming. This disease is regarded as a genuine health problem in several nations of the Maghreb region, India, Middle East, and in America from the Southern United States down to Argentina, according to its prevalence and severity. The severity of scorpion envenoming is influenced by late medical intervention for patients as well as other environmental variables.

4.1. Venoms and Toxicity

The early symptoms observed in envenomed individuals can be explained by the very toxic and quick-acting nature of scorpion venom. Biochemical analysis of scorpion venom revealed a complex makeup containing both deadly and harmless components.

Mucopolysaccharides, enzymes (such as phospholipases and hyaluronidase), protease inhibitors (enzyme inhibitors), and bioamines, namely serotonin and histamine, make up the harmless portion. The principal reason of the deadly venom effects is the neurotoxins of scorpion venom, which have a great affinity for electricity-dependent Na+ channels in excitable cells. Despite sharing a significant degree of identity in their sequences, these neurotoxins differ in terms of how poisonous they are and how well they attach to certain target animal species (sodium, calcium, potassium, or chloride channels) (28) The

activation of these channels is guided by action potential. The latter is launched and passed across the membrane by these channels, boosting sodium permeability.

Neurotoxins extend the action potential reaching the neuromuscular cells by activating voltage-gated Na+ channels and blocking K+ channels, enforcing a slower phase of inactivating sodium channel by engaging with either the third or the fourth membrane site of the channel (29). These events cause a significant release of neurotransmitters and a massive influx of extracellular sodium, which is followed by adrenergic inhibition of membrane excitability. Thus, a significant influx of intracellular calcium was induced by an increase in sodium permeability. Therefore, electrolyte imbalance activates the phospholipases responsible for phospholipid membrane breakdown (11). This may result in widespread symptoms, such as neurological problems, cardiac discomfort, localized pain, and inflammation.

4.2. Symptoms of Scorpion Toxicosis

Depending on the scorpion species and the quantity of venom being injected, certain clinical signs may be observed following scorpion envenomation. The earliest symptoms ranged from local indicators, such as vomiting, nausea, numbness, and inflammation, and progressed to shock-related symptoms, such as cardiovascular issues. Three classes were developed based on the observed indicators and their amplitudes for the classification of clinical manifestations based on rising severity. There is no temporal relationship between these symptoms, which may be mild, moderate, or severe (30).

4.3. Pathology Brought By Envenomation

The complicated biochemical changes and disturbances caused by scorpion venom. Neurotoxins are not the only biological routes that have pathophysiological consequences; other biological pathways are also engaged in the severity of the illness. The neurological system can be compromised in conjunction to cardiovascular problems, acute pulmonary edema, and tissue damage associated to metabolic changes identified following severe accidental or experimental scorpion envenomation. Seizures, heat, hypothermia, irritability, restlessness, tremors, paralysis, and coma are all symptoms of neurological diseases. These occurrences are occasionally accompanied by biological diseases such as hypocalcemia, leukocytosis, and hyperglycemia (5).

4.4. Venom-Induced Anatomical and Pathological Effects

Experimental scorpion envenomation causes a variety of tissue damages that are characterized by profound organ changes. The most striking repercussions were seen in the lungs, where there was extensive disruption to the barrier between pulmonary alveoli and capillaries, interstitial and alveolar edema arising from leukocytosis, transmigration of epithelial cells, and significant fibrin deposits that led to thrombi, and necrosis. Almost all organs, including the vital organs had their tissues damaged (31). The venom of scorpions, such as that of Androctonus australis, disrupts the cardiac fibers and alters the hepatic, pulmonary, and renal parenchyma, causing necrotic regions, interstitial edema, bleeding into the interstitial space, and polynucleated cell infiltration. The cardiac fibers, liver, lung, and renal cortex all experienced the same disarray as a result of centruroides venom. The kidney is a target organ for many poisons because it is crucial for filtration and elimination of hazardous substances and their metabolites. Additionally, after administering centruroides venom intramuscularly, morphological alterations in the glomeruli and tubules are frequently observed (32). As per research studies, venom harms the lungs acutely, resulting in altered lung functions and increased inflammation within the lungs. The main pathogenic mechanism is pulmonary capillary endothelial failure, which leads to edema of exudative fluid rich in phagocytic immune cells and occurs in the interstitial space and alveoli. Pulmonary edema may develop immediately after a sting. Pulmonary edema symptoms may vary, although they can appear rapidly (33).

5. Treatment of Scorpion Envenomation

Understanding and controlling the processes underlying these implications may assist to better implement efficient therapeutic measures in mild to moderately severe instances of envenomation in order to combat this. A retrospective study at the emergency unit of Sultan Qaboos University Hospital (SQUH) revealed that the majority of scorpion stung patients handled exhibited local symptoms. Tachycardia is the most frequent systemic symptom. Infiltration of a local anesthetic is the suggested treatment for scorpion stings. The request for a bedside clotting test was mostly made by junior clinicians and was infrequently requested. Local anesthetic infiltration was used as a secondary therapy after analgesia. Seldom is scorpion antivenom employed (34).

5.1. Therapeutic Measures

An efficient therapeutic approach based on an understanding of the contributing pathways to the established pathophysiological disorders is necessary for the treatment of envenomed patients. There are various recommended approaches for treating scorpion envenomation, from symptomatic care through vaccination. Treatment is complex and contentious in every encountered situation, particularly when antivenom use and concomitant symptomatic therapies are implicated.

5.2. Management of Symptoms

To replace the water lost via vomiting and diarrhea, symptomatic therapy is utilized to maintain vital processes including blood pressure and hydration management. Vasodilators, anti-cholinergics, anti-emetics, anticonvulsants, and antipyretics must be administered. Anti-inflammatory medications like corticosteroids, antihistamines, and aprotinin are also advised to control the inflammatory response and avoid some tissue damage (5).

Lidocaine, an inhibitor of sodium channel, might be more advantageous than symptomatic treatment for the later block of the several neurotransmitters and modulators produced after scorpion envenomation (35).

5.3. Anti-venom Therapy

Immunotherapy is a specialized treatment that is necessary because of the severity of scorpion envenomation and the rapid spread of inoculation venom following stings. Currently, there is commercially accessible anti-venom treatment for several poisonous scorpion species. This therapeutic approach has been recommended as an exclusive method for treating scorpion stings (36). However, the adoption of intensive treatment and symptom management without antivenom led to a dramatic drop in the mortality rate (37, 38, 39, 40, and 41). The selection of antigens from hazardous venom fractions is another factor that can enhance immunotherapy. After administering numerous injections of a poisonous fraction to immunize them, the neutralizing effects of antibodies seemed to be greater than those from the entire venom.

Most modern antivenoms are composed of immunoglobulin fragments. Immunotherapy treating envenomation patients typically uses horse-derived antibodies, and the unstable elements are F(ab0)2 fragments that are administered in an intravenous fashion. However, many issues surrounding immunotherapy require improvement. The timing, route, and dose of antibody injections are only a few instances of the parameters that must be carefully evaluated and monitored when neutralizing antibodies are developed to neutralize the deadly effects of venom.. These necessary factors also include the selection of animal producers, the antigen used to immunize the animals, the neutralizing molecule produced, and the circumstances under which it is applied (42).

6. Conclusion

Most scorpion stings result in localized discomfort and inflammation. If the venom affects sodium channels, the patient might develop seizure-like behavior and complicate the clinical persepctive, especially if the child or baby cannot offer a thorough history. These patients may need to be intubated

because of the possibility of diaphragmatic and intercostal neuromuscular activity as well as motor hyperactivity of the pharyngeal muscles. These signs may develop rapidly and signal imminent airway collapse. Cardiogenic shock, tachycardia, and pulmonary edema may occur in specific species that cause cardiopulmonary consequences. Although rare, local tissue necrosis has been observed days to weeks after the original stung.

Platelet-activating factor, nitric oxide, and cytokines are among the mediators of inflammation released in response to scorpion envenomation. The production of these mediators and additional ones is thought to be the root of acute respiratory distress syndrome (ARDS), systemic inflammation, and multiple organ dysfunction. A deeper comprehension of the pathophysiological effects brought on by scorpion envenomation, particularly those owing to hemodynamics, tissue alterations, and inflammatory responses, could result in the development or adaptation of novel therapeutic approaches or new medications to effectively treat and manage envenomed patients despite their late arrival admission to medical facilities.

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