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Effect of animal venom toxins on the main links of the homeostasis of mammals (Review)

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Abstract. The human body is affected by environmental factors. The dynamic balance between the organism and its environment results from the influence of natural, anthropogenic and social aspects. The factors of exogenous origin determine development of adaptive changes. The present article summarises the mechanisms of animal venom toxins and homeostasis disruption in the body of mammals. The mechanisms underlying pathological changes are associated with shifts in biochemical reactions. Components of the immune, nervous and endocrine systems are key in the host defense and adaptation processes in response to venom by triggering signalling pathways (PI3kinase pathway, arachidonic acid cascade). Animal venom toxins initiate the development of inflammatory processes, the synthesis of pro-inflammatory mediators (cytokines), ROS, proteolytic enzymes, activate the migration of leukocytes and macrophages. Keratinocytes and endothelial cells act as protective barriers under the action of animal venom toxins on the body of mammals. In addition, the formation of pores in cell membranes, structural changes in cell ion channels are characteristic of the action of animal venom toxins.

Contents

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1. Introduction

The human body is affected by environmental factors (such as bacteria, viruses, climate, toxins). The dynamic balance between the organism and its environment results from the influence of natural, anthropogenic and social aspects. The action of any elements of exogenous origin determines the development of adaptive changes. Almost all organs and systems forming these adaptive mechanisms, the coordinated activity of which maintains stability in the internal environment, known as homeostasis (1). Homeostasis is provided by normal functioning of the immune, nervous and endocrine systems. Maintaining the stability of the internal environment must be considered not only at the tissue, organ and system levels but also at the molecular and cellular levels since this is where the primary response to the action of external agents begins. Maintaining dynamic balance depends on how long the damaging factors act (2). The organism can show self-regulation, reactivity and stability. However, damage to the structural and functional components of the systems that ensure the maintenance of homeostasis leads to disruption of coordinated activity and pathological reactions (3,4).

Among the factors affecting the homeostasis system, animal venom toxins play an important role. Venoms comprise proteins, peptides, biogenic amines and salts produced by various species of animal for protection or hunting prey. However, in the case of bites of venomous animals, the body receives numerous toxins that are distributed in the skin, blood vessels, skeletal muscle fibres, and organs (5). Typically, venoms containing substances of a protein nature also include minor protein components and a number of organic and inorganic substances, which together determine the physiological activity and nature of the toxic effect (6). Animal venoms usually include enzymes (hyaluronidase, phospholipase A, nucleotidase, phosphodiesterase, deoxyribonuclease, L-amino acid oxidase, acid phosphatase and acetylcholinesterase), proteins with specific properties (nerve growth and anti-complementary factor), hemotoxins, neurotoxins, biogenic amines (serotonin and histamine), monosaccharides and polysaccharides (7).

2. Mechanisms of disruption of cellular homeostasis of mammals following animal venom toxin exposure

Cells of the immune system are the first barrier to pathogenic factors. Membrane receptors recognise changes in the intercellular matrix and signal disruption of the homeostasis system and the initiation of compensatory signalling cascades. The mechanisms of the cellular response to the action of certain stimuli depend mainly on the duration of disturbances in homeostasis. There are four stages of the cellular response (3,4). During the first, changes occur in phosphorylation and dephosphorylation of key regulatory proteins to restore impaired body functions or adapt to the changes. The second stage involves activating the expression of fast-response genes. At this stage, it is possible to recognise unfolded proteins due to folding disorders in the endoplasmic reticulum (ER) and the development of stress. Under stronger and prolonged exposure to damaging agents, damage to the structure of organelles) occur due to reprogramming of their genome and the concentration on eliminating pathological changes (3-5). These processes characterise the third stage of the cellular response. At the fourth stage, activation of cell apoptosis mechanisms mediated by ER stress or development of compensatory and adaptive changes to a constantly acting stressor occurs. The mechanisms of cell response are aimed at survival and preservation of the organism (8,9).

Action of toxins of various origins, including the components of animal venom, disrupt normal functioning and induce structural rearrangements of organs (7). There are numerous venomous animals with insufficiently studied proteome, peptidome and biological activity that are the focus of an increasing number of experimental studies (7,8).

The effects of venom range from mild clinical symptoms to death. Symptoms of venom are divided into local and systemic. Local symptoms include reddening of the skin at the site of bite, swelling and enlargement and swelling of lymph nodes. Systemic manifestations include nausea, vomiting, sweating, bleeding, fever, difficulty breathing and anaphylaxis. Disturbances of normal functioning of the lymphatic system, the development of lymphadenitis and neuromuscular fasciculations are long-term consequences of venomous animal bites (9,10). Toxins leads to the activation of the immune system, which ensures the formation of compensatory and adaptive changes (Fig. 1). Its dysregulation, mediated by the action of the venom, can cause severe complications or even death (11,12).

To protect against the components of animal venom, a quick reaction is essential and is achieved by the coordinated work of the innate immune system. The mechanisms include blood-tissue barriers for an immediate but non-specific response to the action of toxins. Physical barriers, such as skin and mucous membranes, as well as a set of chemicals, including enzymes, that interact with resident and migrating cells, are key in the host response. In response to any stressor, the activation of pro-inflammatory mediators such as cytokines and chemokines is observed (1-3). In addition, numerous cells of the immune system are activated, migration of leukocytes to the affected area is initiated and the production of reactive oxygen species (ROS), reactive compounds of nitrogen oxide (NO) and numerous proteases are generated, ensuring maintenance of the regulation of innate effector functions and homeostasis (13-16).

Key components of an innate immune response are keratinocytes of the epidermis, which act as the first barrier when bitten by venomous animals. Keratinocytes play a protective and pro-inflammatory function and their cross-interactions with the cells of the dermo-epidermal junctions underlie regulation of immune cell maturation processes at the initial and late stages of inflammation (17-19). Similar to cells of the immune system, keratinocytes express receptors for cytokines and pattern recognition receptor (PRR) proteins that can recognise common molecular structures, such as venoms. Their activation under the action of the components of animal venom initiates synthesis and release of cytokines, NO and alarmins (endogenous constitutive, chemotactic and immune-activating peptides that are released in case of injury or cell death or in response to induction of the immune defence system) (20,21). These processes cause the formation of foci of inflammation and involvement of numerous cells, both resident and migratory (22). Proteolytic enzymes induce the death of keratinocytes by apoptosis or necrosis (23,24). The proteolytic degradation of structures of the epidermis and dermis ensures the access of venom components to the blood circulation, lymphatic system and target organs. Apoptosis of keratinocytes may lead to excessive expression of endogenous MMPs, which indirectly triggers the destruction of tissues at the bite sites. Bites of the *Loxosceles rufescens* spider cause key dermonecrotic consequences, systemic inflammatory reaction and even fatal consequences, especially among children. In this case, the pathophysiological mechanisms of action of toxins are attractive, which consist in the stimulation of apoptosis of epidermal cells by the enzyme sphingomyelinase D, which increases the synthesis of membrane-bound MMP-2 and MMP-9 in cell culture (25-28).

Endothelial cells of the walls of blood vessels also play an essential role in recognising and protecting the body from toxins. As the main point of contact with toxic components of natural venoms that have entered the bloodstream, endotheliocytes perform the function of recognising them by expressing numerous PRRs, among which toll-like receptor (TLR), TNF receptors and IL-1 and cause activation of pro-inflammatory genes and pathological changes in the microcirculation of blood vessels (26,27). Endotheliocytes also express molecules of the major histocompatibility complex (MHC) classes I and II and CD40 ligands, ensuring intravascular presentation of foreign agents, including animal venom toxins, to effector cells of the immune system (28). Endothelial cells modulate function of the immune system by affecting migration of leukocytes. Adhesion and extravasation of leukocytes are characteristic phenomena in response to highly selective expression of cell adhesion molecules-1 and selectin on the apical surface of endotheliocytes. Endothelial dysfunction as a result of venom toxins, characterised by distortion of structure and functions of endothelial cells leads to changes in the immune response. Rat experiments have proven a violation of the permeability and stability of vessel walls under endothelial dysfunction. In the case of snake and spider venoms, an increase in secretion of IL-6 and 8 and monocyte chemoattractant protein-1 (MCP-1) is also observed *in vitro* in culture of endothelial cells (29,30). With increased production of these compounds, neutrophils

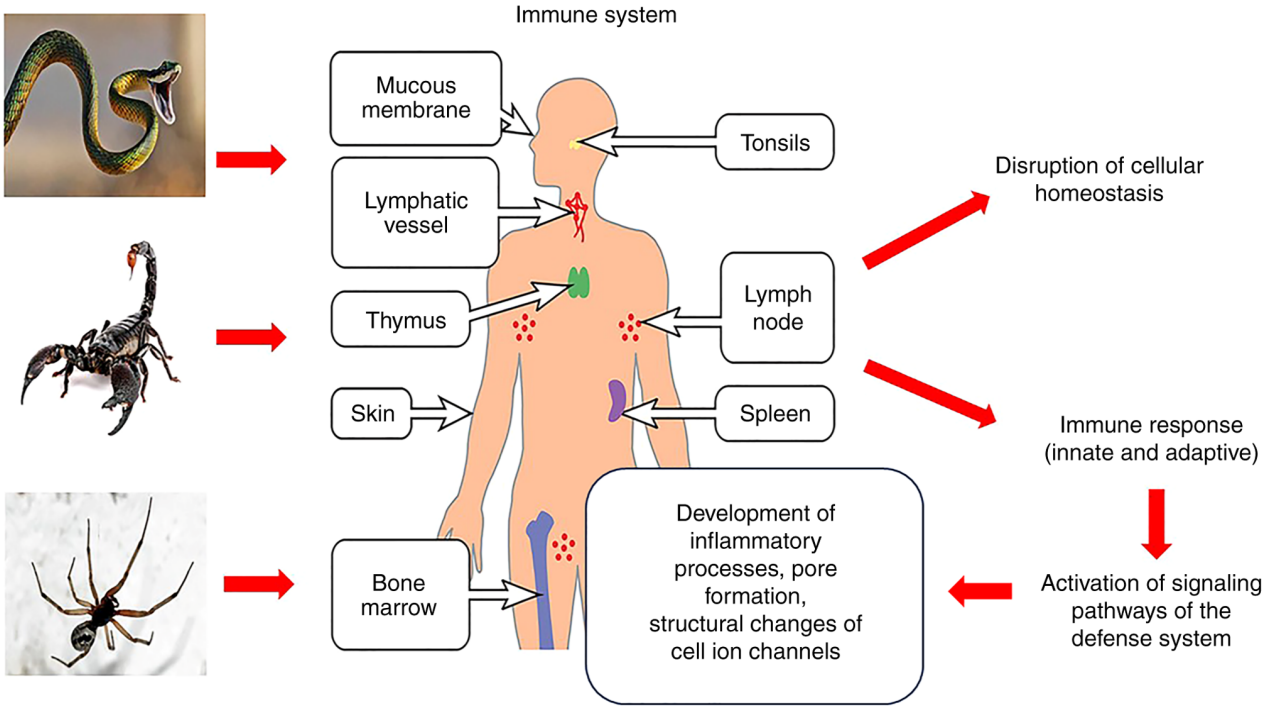

Figure 1. Influence of animal toxins on the immune system of the human body. Activation of the of the immune system in response to the action of the animal venom toxins, disruption of cellular homeostasis, activation of protective and adaptation mechanisms of the human body.

exhibit adhesive properties in relation to endotheliocytes through selectin-mediated connections, and this notably increases intracellular levels of Ca^{2+} and release of proteolytic enzymes responsible for tissue degradation (30,31).

The monocyte-macrophage system (MMS) is a key component of innate immunity. Most animal toxins disrupt the structure and function of MMS cells (32). Toxins of *Crotalus durissus terrificus* viper decreases migratory and phagocytic ability of macrophages in the peritoneal cavity of rats. The crotoxin of their venom has enzymatic properties and is capable of significantly decreasing the expression of MHC type II molecules that presenting foreign agents to T lymphocytes, as well as costimulatory molecules such as CD40, CD80 and CD86. In addition, crotoxin inhibits the production of IL-6, TNF-α and IL-12 and interferes with the phosphorylation of NF-κB and MAPK p38. However, it stimulates production of IL-10, TGFβ and prostaglandin E2 (PGE2) and phagocytic activity of macrophages and causes toxin-mediated changes in cytoskeleton proteins of these cells. The effect of crotoxin is accompanied by production of NO in macrophages by activation of inducible NO synthase (iNOS). Under these conditions, glucose metabolism and the amino acid glutamine are disturbed in the cells due to induction of hexokinase, glucose-6-phosphate dehydrogenase and glutaminase. Such enzymatic hyperactivity in macrophages is associated with an increase in levels of ATP and numerous metabolites, as well as stimulation of the inflammatory response, primarily via the production of NADPH (32,34). NADPH serves as a substrate for $NADPH^+$ oxidase and ROS secretion, in particular, H_2O_2 (33-35). Other studies show that the venom of *Bothrops alternatus* snake increases the phagocytic activity of macrophages and their production of superoxide radicals, which are involved in tissue destruction at the sites of bites (35-37). Experiments on mice using macrophage cell culture revealed powerful pro-inflammatory properties (36,37). In particular, *Androctonus crassicauda* scorpion toxin induces expression of IL-12p40 mRNA, which is a chemoattractant of macrophages that stimulates migration of dendritic cells and is associated with activation of the inflammatory cascade (38-40). Toxins Ts_1 and Ts_6 of *Tityus serrulatus* scorpion contribute to the production of NO and H_2O_2 in macrophages and modulates the inflammatory response, characterised by an increase in the blood levels of TNF-α, IL-6, IL-1α, IL-1β and IL-8 (41-43) in rats. C-type lectin-like proteins obtained from the venom of *Bothrops jararacussu* snake enhance production of TNF by macrophages and the activity of CD14 without affecting the proliferative capabilities of these cells (44). Sphingomyelinase D in *Loxosceles laeta* spider venom promotes macrophage migration and cytokine release by skin fibroblasts. *Bothrops* snake toxins stimulate secretion of pro-inflammatory mediators, PGE2, macrophage inflammatory protein-1 (MIR-1) and IL-1β and NF-κB activation in cultured human MMS cells (45,46). Therefore, the components of the venom of various species of predatory animals exert an immunostimulating effect on the MMS and contribute to development of a systemic inflammatory response (47-49).

Neutrophils are involved in rapid response to the inoculation of animal venom toxins. Like other cells of the immune system, they are potent producers of cytokines and chemokines capable of activating pro-inflammatory mechanisms. Following bites of venomous animals, exocytosis of secretory granules of neutrophils, containing ~700 different proteins, mainly enzymes, that enter the extracellular matrix, is characteristic (50,51). Defensins, serine proteases, neutrophil elastase, proteinase 3 and cathepsins are among the main enzymes capable of inactivating the toxic components of

venom through their proteolytic degradation (50). The role of proteolytic enzymes in the degradation of necrotic tissues has also been established. Studies have demonstrated the role of neutrophils in stimulating the programmed death of cells affected by venom of predatory animals (52-55).

Studies have demonstrated that TLR_2 and TLR_4 serve a key role following bites of venomous animals (35,56-58). They recognise various toxins of animal venoms, for example, Ts_1 venom of *T. serrulatus*. Ts_1 belongs to β-toxins that bind to TLR_2 and TLR_4, inducing the production of cytokines and lipid mediators and triggering the inflammatory cascade. The latter is associated with activation of NF-κB, transcription factor-1, which regulates gene expression in response to numerous signals, including stress damage, and controls cell differentiation, proliferation and apoptosis. In addition, increase in MAPK, which is responsible for gene transcription, proliferation and migration of cells and their apoptosis, is characteristic (56,57). Secretory phospholipase ($sPLA_2$), a component of the venom of *Bothrops atrox* and *Bothrops asper* snakes, recognises TLR_2, leading to production of eicosanoids such as PGE2 and leukotrienes. Leukotrienes act as powerful chemoattractants of neutrophils to the site of venom entry. TLR_2 also stimulates the migration of polymorphonuclear leukocytes and production of IL-1β under the conditions of intraperitoneal injection of *B. atrox* snake venom to laboratory rats (35,58,59).

Tissue basophils, stimulation of which is associated with inflammasome activation and caspase-1 expression, serve an essential role in the mechanisms of the immune response to venomous animal toxin (60,61). In addition, they release histamine and lipid mediators, and their degranulation can cause development of an anaphylactic reaction (62). Congenital anomalies of basophils, including mutations in mastocytosis, are causes of severe allergic reactions of the body to animal bites and fatal consequences. Thus, it has been demonstrated in rats that the toxins of *B. atrox* snakes induce formation of fractions of the complement system C3a and C5a, which contribute to degranulation of tissue basophils, chemotaxis, activation of neutrophils and the development of severe anaphylaxis (63-70).

3. Molecular structure and mechanism of action of toxins of venomous animals

In Brazil, 26,000 snakebites were reported in 2016, with 109 deaths. The annual snakebite mortalities in India are 46,000, in Bangladesh-2 6,000 and 400 in Sri Lanka. The number of isolated and identified animal toxins is increasing every year (25). Therefore, researching their molecular structure and mechanism of action is urgent. Most act by modulating the main signalling cascades (PI3kinase pathway, arachidonic acid cascade) of cells or directly interfering with ion balance, which is maintained by cell membranes (71). Certain types of toxin penetrate the bilipid layer of the plasmalemma, forming pores. By contrast, others act on ion pumps or channels responsible for maintaining the concentration gradients of ions (72). The molecular mechanisms underlying the effect of animal venom on signalling cascades are that their toxic components are directed at individual target points of cell membranes, where, under normal conditions, secondary messengers initiate a physiological response to stimuli. When interacting with toxins, complex pathways of biochemical reactions are suppressed, which causes a pathological response in host cells. Plasmolemma targets of venoms include ligand-gated ion channels, G protein-coupled and tyrosine kinase receptors, integrins and specific lipids (73,74). Certain targets (receptors, ion channels) are located inside cells, particularly in organelles capable of forming a specific response to the action of the toxin. Currently, two mechanisms of target changes at the level of host cell membranes are known. The first consists of conformational changes of receptors, opening of ion channels for the flow of ions and depolarisation of the cell. The second mechanism is translocation, which involves stimulus-induced movement of transporters of certain compounds from cells to domains of the outer surface of the plasmalemma (75-79).

With interaction between the components of animal venoms and the host, processes such as energy metabolism, post-translational changes, cytoskeleton stability, gene expression, motility, secretion, cell division and specific functions are disturbed. Under normal conditions, communication between cells and natural ligands leads to controlled changes in intracellular levels of second messengers such as cAMP, Ca^{2+}, inositol triphosphate and 1,2-diacylglycerol. Protein kinases activated by these messengers phosphorylate numerous molecules of the cellular substrate, stimulating signalling pathways (80). However, when the triggering of these mechanisms is caused by non-physiological factors, such as animal venom toxins, the cascade of signalling pathways is disrupted, leading to the development of pathological changes in cells that can ultimately lead to their death. Toxins typically enhance or inhibit the activity of proteins and enzymes, which disrupts cellular homeostasis. Cell homeostasis is ensured mainly by the integrity and stability of the plasmalemma. This process is dynamic and regulated by cells to compartmentalize and protect organelles and genetic material in the nucleus. The primary requirement for membrane integrity is the preservation of ion concentration gradients. The penetration of animal toxins into the double lipid layer and the formation of pores lead to a change in the concentration of ions and the death of cells (81-83).

Pore-forming toxins are polypeptides that contain both a hydrophilic/polar domain and a hydrophobic/nonpolar domain that vary in size from small peptides and oligomers to large macromolecules. These animal venom toxins increase permeability and/or destroy the plasma membrane. Pardaxin, produced by certain marine fish, exerts its effects through hydrophobic/lipophilic interaction with phospholipids of biological membranes of host cells and the formation of pores. This is associated with colloid-osmotic changes in the cell, particularly swelling. In addition, pardaxin stimulates the increase of the intracellular levels of Ca^{2+}, activation of PLA_2, the production of eicosanoids and numerous endonucleases, the release of cytokines, the initiation of inflammatory mechanisms and apoptosis (84-88).

Most venomous animal toxins contain $sPLA_2$, which enhances the activity of PLA_2 cell membranes or mimics the action of endogenous PLA_2. This enzyme is key in the metabolism of phospholipids in cells, primarily in the hydrolysis of phosphatidylcholine with the formation of lysophosphatidylcholine and arachidonic acid. The PLA_2 family includes $sPLA_2$, cytosolic Ca^{2+}-activating and several Ca^{2+}-independent isoforms. Under physiological conditions, the action of these

enzymes on membrane phosphatidylcholine is accompanied by the release of arachidonic acid, which is converted into phosphatidylcholine or oxidised by alternative pathways with the participation of cyclooxygenases, lipoxygenases and cytochrome P450-like epoxygenases, which is accompanied by formation of prostaglandins, leukotrienes and thromboxanes. Thromboxanes participate in regulation of various body processes (vasoconstriction, increased blood pressure, platelet aggregation). However, excessive amounts of PLA_2 from animal venom or increased enzyme activity lead to pathological reactions and cell death). Venoms may contain notable amounts of melittin, produced by insects, and crotoxin, which snakes produce. In particular, the crotoxin of Brazilian snake *Crotalus durissus terrificus*, acting on the structure of the cell membranes via secretion of PLA_2, contributes to penetration of highly active toxins, causing a neurotoxic effect aimed at the presynaptic endings of neuromuscular junctions (89-91). This blocks the release of acetylcholine and reduces the number of synaptic vesicles. Crotoxin can affect postsynaptic membranes by binding to nicotinic cholinergic receptors, preventing conformational changes. Its cytotoxicity has been proven on cultured cell lines (endothelial cells) (32-36). It shows high selectivity in cell lines that express epidermal growth factor receptors (92,93). Melittin does not show the high enzymatic activity of PLA_2. Melittin induces endogenous enzymes by binding to membranes through hydrophobic interactions with zwitterionic phospholipids, disrupting the orientation of the phosphate group to alter properties of phospholipids and ultimately weakening the barrier function of the plasmalemma. Formation of melittin-phospholipid domains on the surface of erythrocytes causes hemolysis (94-100).

Toxins of venomous animals have a pathological effect on the ion channels of cell membranes. Under normal conditions, these ion channels regulate transport of cations and anions, maintain resting membrane potential and control action potential in cells. Given the importance of ion concentration gradients supporting the functioning of nervous, cardiac, skeletal and smooth muscle tissue, many toxins have been investigated that are capable of modulating the conductance and/or kinetics of ion channels, serving as channel-opening or blocking agents (101-104). In non-excitable cells, ion channels regulate transport of nutrients, release of certain compounds and activation of cells of the immune system. Most ion channels (Na^+, K^+, Ca^{2+} and some Cl^-) are voltage-dependent, while others are insensitive to voltage changes and are controlled by second messengers or intracellular or extracellular mediators. Voltage-dependent ion channels open or close depending on the concentration gradient on both sides of the plasma membrane. Ions pass through channels according to their electrochemical gradient. Toxins of scorpion and snake venoms selectively change the activity of such channels (105-112). Experimental studies have demonstrated that dendrotoxins produced by several species of African snake (*Dendroaspis angusticeps, viridis* and *polylepis*) block potential-dependent K^+ channels in neurons (108-111). The effect of dendrotoxins increases release of acetylcholine in neuromuscular junctions. In the nervous system, potential-dependent K^+ channels are responsible for membrane repolarisation and control duration of the action potential. Dendrotoxins bind to K^+ channels of Ranvier intercepts of motoneurons, blocking their activity. This increases duration of the action potential and release of acetylcholine in synapses, leading to excessive overexcitation and convulsions (113). The molecular mechanisms underlying the interaction between dendrotoxins and potential-dependent K^+ channels are that their communication is initiated by electrostatic connections between positively charged amino acid radicals in the cationic region of dendrotoxin and negatively charged radicals in the pores of ion channels. K^+ channels have areas of negative charges localised at the front of the channel. Dendrotoxin molecule is also capable of mechanically blocking the channel pore. However, certain data suggest that dendrotoxin blocks the channel by conformational changes in its structure (114,115).

α-toxins of scorpion venom are potential-dependent Na^+ channel blockers. They can bind to the α-subunit, the site of receptor three, and induce action potential prolongation in excitable tissue by blocking transition of the channel from the open to the closed state, showing high selectivity for mammals. The binding of the toxin to the Na^+ channel prevents the structural changes necessary for rapid inactivation, thereby enhancing excitation (116-119).

Scorpion venoms are also tropic to Cl^-channels involved in regulating cell volume, muscle contraction, secretion and modulation of neuronal signal transduction. The passive flow of Cl^-anions through biological membranes is regulated by interaction with ligands, changes in intracellular Ca^{2+} levels and membrane potential. One example is chlorotoxin, a peptide isolated from the venom of deathstalker scorpion (*Leiurus quinquestriatus).* Chlorotoxin is a high-affinity ligand that blocks chloride channels. In addition, chlorotoxin increases expression of MMP-2 isoforms by brain glioma cells (120-123).

4. Conclusion and future perspectives

Toxic compounds of animal venom penetrating disrupt the stability of the internal environment. The mechanisms underlying pathological changes are associated with changes in the structure, function and biochemical reactions. The first line of defence against the negative effects of toxins is cells that contribute to the restoration of damaged links of homeostasis or the formation of specific adaptations. Toxins of various species of venomous animals can interfere with the morpho-functional properties of cells, destroying their protective membranes, forming pores or disrupting the activity of ion channels. Components of the immune, nervous and endocrine systems are key in defense and adaptation processes in response to venom by triggering signalling pathways. Coordinated activity supports the vital functions and the dysfunction causes serious or fatal consequences. Therefore, studying changes in the homeostasis, primarily at the cellular level, under these conditions is key.

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Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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