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Ivanitsa Arina Oleksandrivna associate professor of the Pathophysiology Department, National Pirogov Memorial Medical University, Vinnytsia, https://orcid.org/0000-0002-4115-9638

PATHOPHYSIOLOGICAL MECHANISMS OF ACTION OF SNAKE VENOM

Abstract. Snakebite is a major health issue worldwide, particularly affecting rural and tropical areas where medical facilities are scarce. Snake venom is a complex mixture of biologically active substances that can lead to serious hemostatic, neurotoxic and necrotic complications. The high mortality rate, particularly in South Asia and Africa, is the result of both strong venom toxicity and delayed treatment seeking by victims. The purpose of this review is to summarize the information on snake venom composition, its pathophysiological effect and situs actionis of active compounds. Materials and methods a search of literary resources in the Google Scholar, PubMed and Scopus data bases was made (30 publications were selected). Venom from snakes is a complex pool of biological substances consisting of enzymes (phospholipase A2, metalloproteinases, serine proteases), toxic proteins (cytotoxins, neurotoxins and cardiotoxins) and low molecular weight molecules which produce local or systemic reactions. Toxins easily get into the blood or lymph glands and half-life of separate elements may be up to 10-60 hours. Cell membranes and necrosis are damaged, which lead to inflammation by PLA2 and cytotoxins. Vascular basement membrane is destroyed by metalloproteinases (notably class P-III), which results in hemorrhage, edema and microangiopathy. Neurotoxins and cardiotoxins competitively inhibit acetylcholine receptors or ion channels resulting in paralysis and arrhythmias. Similarly, serine proteases alter coagulation cascades usually resulting in thrombosis or consumptive coagulopathy. L-amino acid oxidases generate hydrogen peroxide, are toxic to cells and possess antimicrobial activity. Metalloproteinases also mediate the release of IL-1β, TNF-α and IL-6 in a process that activates the local inflammatory response. Snake venom is therefore a mixture of pathophysiologically active compounds with many toxins having multifunctional roles. Comprehensive study of the mechanisms of action of these animals provides an opportunity to perfect methods for treatment on intoxications and opens prospects for the development of new drugs.

Keywords: snake venom, pathophysiological mechanisms, neurotoxins, hemotoxins, coagulopathy.

Іваниця Аріна Олександрівна доцент кафедри патологічної фізіології, Вінницький національний медичний університет ім. М. І. Пирогова, м. Вінниця, https://orcid.org/0000-0002-4115-9638

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ПАТОФІЗІОЛОГІЧНІ МЕХАНІЗМИ ДІЇ ОТРУТИ ЗМІЙ

Анотація. Укуси змій є серйозною проблемою охорони здоров'я в усьому світі, особливо в сільських та тропічних районах, де медичних закладів не так багато. Зміїна отрута являє собою складну суміш біологічно активних речовин, яка може призвести до серйозних гемостатичних, нейротоксичних та некротичних ускладнень. Високий рівень смертності, особливо в Південній Азії та Африці, є результатом як сильної токсичності отрути, так і несвоєчасного звернення потерпілих за допомогою. Метою цього огляду є узагальнення інформації про склад зміїної отрути, її патофізіологічний ефект та місце дії активних сполук. Матеріали та методи: було проведено пошук літературних ресурсів у базах даних Google Scholar, PubMed та Scopus (було відібрано 30 публікацій). Отрута змій являє собою складний пул біологічних речовин, що складається з ферментів (фосфоліпаза А2, металопротеїназ, серинових протеаз), токсичних білків (цитотоксинів, нейротоксинів та кардіотоксинів) та низькомолекулярних молекул, які викликають місцеві або системні реакції. Токсини легко потрапляють у кров або лімфатичні залози, а період напіврозпаду окремих елементів може сягати 10-60 годин. Клітинні мембрани та некроз пошкоджуються, що призводить до запалення, викликаного PLA2 та цитотоксинами. Базальна мембрана судин руйнується металопротеїназами (особливо класу P-III), що призводить до крововиливу, набряку та мікроангіопатії. Нейротоксини та кардіотоксини конкурентно пригнічують ацетилхолінові рецептори або іонні канали, що призводить до паралічу та аритмій. Аналогічно, серинові протеази змінюють каскади згортання крові, що зазвичай призводить до тромбозу або коагулопатії споживання. L-амінокислотні оксидази генерують перекис водню, є токсичними для клітин та мають антимікробну активність. Металопротеїнази також опосередковують вивільнення IL-1β, TNF-α та IL-6 у процесі, який активує місцеву запальну реакцію. Зміїна отрута, таким чином, є сумішшю активних сполук з багатьма токсинами, які мають багатофункціональні ролі. Всебічне вивчення механізмів дії отрути цих тварин дає можливість удосконалити методи лікування інтоксикацій та відкриває перспективи для розробки нових ліків.

Ключові слова: зміїна отрута, патофізіологічні механізми, нейротоксини, гемотоксини, коагулопатія.

Statement of the problem. Venomous snakes are a group of reptiles that can produce secretions with toxic substances in specialized glands that enter the victim’s body with the help of teeth. This evolutionarily formed apparatus allows not only to help snakes hunting but also performs a protective function. The greatest medical significance is attributed to representatives of the families Elapidae (such as cobras, mambas) and Viperidae (in particular, vipers and cobras), whose venom contains various components that can cause severe systemic disorders, including humans [1].

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Venomous snakes are distributed on all continents except Antarctica, but their greatest prevalence is found in tropical and subtropical regions. The distribution and toxicity of snakes have a certain specificity, which allows us to identify endemic areas of increased risk of bites [2]. According to a systematic review, hemotoxic and neurotoxic lesions remain the most common types of poisoning after snake bites. Hemotoxic forms of venom are more common in tropical Africa and South Asia. At the same time, neurotoxic types of snake venom are more common in Southeast Asia, in particular, bites from krait and cobra. Metadata also shows that most cases of poisoning occur in rural areas with limited access to medical care [3].

For example, a study in Kenya showed that snakebites occur with a frequency of 151 cases per 100,000 population per year, and more than 30% of victims do not seek help, preferring traditional methods of treatment [4]. In Nigeria, more than 50% of bites are recorded among able-bodied men aged 15-44 years. Most often, bites occur during agricultural work. The proportion of hospitalizations due to snakebites in some regions exceeds 60% of all poisoning cases [5].

The same predominant localization of snakebites is observed in rural areas of South Asia. In Sri Lanka, one district recorded an annual incidence of snakebites of 398 per 100,000 population. In this case, in 89.6% of cases, patients had clinical signs of intoxication, with a pronounced local reaction in more than 60% of victims [6]. In Bangladesh, the average rate is 623 bites per 100,000 people per year, and almost half of patients reported systemic symptoms within the first 6 hours after the bite. As in the study from Kenya, a high frequency of use of traditional remedies instead of seeking medical care in a hospital was also found [7].

In Europe, in contrast to the regions mentioned above, the overall incidence of bites is lower, however, a certain seasonal and regional pattern can be traced, especially in the countries of Southern Europe. According to the review, the average annual prevalence of snakebites in France is 1.3 per 100,000, in Italy - up to 1.8, and in the Scandinavian countries - less than 0.5 per 100,000. Fatalities are exceptionally rare, which the authors attribute to the effective provision of medical care and the prompt treatment of victims for medical help [8].

In contrast, India is one of the world leaders in the number of deaths from snakebites. According to the national epidemiological survey, the annual mortality from snakebites reaches about 46,000 people, which is 0.47% of all deaths in the country. Most deaths, as noted earlier, occur in rural areas. Only a third of patients manage to reach the hospital within the first 3 hours after the bite, which is also noted in the mortality rate [9].

In Malaysia, a retrospective study from the Kangar District Hospital reported 260 snakebite cases over a two-year period. The average age of the victims was 26 years, and most patients received only symptomatic treatment due to lack of access to specific antiserum. Despite this, mortality in this region remained low, but the risk of serious complications was high [10].

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Studies in the Terai region of Nepal found an annual incidence of 251 bites per 100,000. About 10% of victims required hospitalization, with a human mortality rate of 3.6 per 100,000. The data highlights the critical role of occupational occupation (over 80% of cases occurred during agricultural activities) [11].

Thus, venomous snakebite is a serious global health problem that is geographically unevenly distributed and requires a multidisciplinary approach to prevention, diagnosis, and treatment.

The purpose of the article – to summarize known data regarding the features of the pathophysiological mechanism of action of snake venoms, the composition of venoms, and the points of application of their active components.

Research objects and methods. A search for literary sources was conducted using keywords within the scientometric databases Google Scholar, PubMed, and Scopus. Keywords and word combinations were used for the search according to the topic of the article. A total of 30 publications were found.

Presentation of the main material.

Research results and their discussion. Snake venom is a very complex substance and consists of biologically active proteins and peptides, which result in systemic or local pathophysiological effects. The enzymes (phospholipases, metalloproteinases and serine proteases), toxic proteins (cytotoxins, neurotoxins and cardiotoxins) and non-protein low-molecular preparations are of primary importance. A number of them are very specific for cell receptors or blood clotting factors so that several pathological cascades are generally activated simultaneously. Besides their toxic advantage, single venom molecules have potential as antithrombotic agents and anticancer and anti-inflammatory compounds [12].

Survival time after snake venom bite depends on the species of snake, kind of venom as well and its route entry. When injected into tissue, toxins quickly pass into the blood stream or lymphatics. In humans, for instance, the half-lives of certain venom components are between 10 and 60 hours. The existence of local tissue necrosis largely determines the rate of absorption, so prognosis and tactics of treatment depend on it as well as [13].

Cytotoxins, PLA2s and metalloproteinases are some of the most potent activities in snake venom. They damage cellular membranes, the extracellular matrix and activate inflammatory pathways. Cytotoxins were is known to work by binding with plasma lipid to breakdown the integrity of plasma membrane and yields necrosis [14]. Phospholipases A2, centrally the Asp49 class, hydrolyze membrane phospholipids and liberate arachidonic acid with subsequent induction of a strong inflammatory reaction [15].

Snake venom metalloproteinases (SVMPs) can degrade vascular bed basement membrane components (including laminin and collagen IV) leading to hemorrhage, increased endothelial permeability and even necrosis. For instance, the P-III-class of Snake venom metalloproteinases possess domains capable of a high degree of substrate specificity to blood vessel wall components. It subsequently induces microvascular

injury, and massive erythrocyte extravasation that is the morphologic cause of hemorrhagic symptoms [16].

Specific binding of monomeric protein fractions to ion channels and receptors can account for neurotoxic and cardiotoxic effects. Other toxins are nicotinic acetylcholine receptor antagonists, which block neuromuscular transmission, resulting in paralysis. The others work on the cardiac potassium or calcium channels, which may disturb myocardial electrophysiology [17].

Enzymatic poisons especially serine proteases are known to model or block the coagulation cascade. They are capable of inducing both hypocoagulation (via fibrinogenolytic activity) and local thrombogenicity via activation of thrombin or factor X. Several venoms have been found to contain enzymes with thrombin-like actions that generate unstable fibrin that is rapidly lysed [18, 19].

Another significant class is L-amino acid oxidases that cause oxidative stress by hydrogen peroxide production. They can trigger apoptosis in different cell types, such as endothelial and immune cells, leading to systemic toxicity. Furthermore, their part in primary inflammatory responses are supported by in vitro studies [20].

The hemorrhagic effect of snake venoms is responsible for due to metalloproteinases which can break down capillaries and microvessels. In particular, SVMPs have also been shown to destabilize interendothelial contacts, inducing interstitial edema and hemorrhages. The severity of injury is a function of the class and concentration of enzyme from spores or existing material as well as its duration of activity [21].

Pain following a snake bite is the result of not only mechanical trauma but also toxin action on nociceptive neurons. One compound in the venom activates TRP receptors or triggers the release of substance P, which increases pain perception. Site of injection also matters: in muscle tissue, pain is usually greater than when the substance injected subcutaneously [22].

The bleeding can be attributed not only to sheer damage of vessels, but also to enhanced activation of the endothelium and platelets. SVMPs may also up-regulate the expression of adhesion molecules and subsequently result in platelet adhesion and secondary inflammation. This is conducive to thrombosis in the context of overall coagulopathy [23].

Cardiotoxins isolated from cobra venom disrupt ionic permeability of cardiomyocyte membranes. They provoke depolarization, enhanced Ca^{2+} entry and arrhythmia. Given in high doses, their effect is necrosis of the heart muscle and this is especially clinically dangerous in patients whose cardiovascular system has some pathology [24].

These so-called thrombin-like enzymes generate unstable fibrin clots which do not have the capacity for a longer lasting polymerization. The consequence is the development of consumptive coagulopathy with clinical appearance of bleeding, while platelet count is normal or low. An analogous effect has been described previously for enzymes present in the venom of vipers of the genus Bothrops [25].

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There are venom constituents with anticoagulant activity binding with prothormbin, factor X or thrombomodulin. This results in an obstruction of fibrin polymerization and a reduction in active thrombin. Homologous mechanisms have been investigated with the Ecarin complex from the venom of Echis carinatus [26].

SVMPs also induce the production of proinflammatory cytokines as IL-1β, TNF-α and IL-6, activating a local cascade of inflammation. Infiltration with neutrophils, matrix degradation and tissue necrosis follow. Such effects are important in generating a local lesion at the bite site [27].

Procoagulative effect Some toxins activate factor X independently of factors VII or tissue factor. It may result in large thrombi in small-sized vessels. They act fast and can be deadly without an antidote [28].

The PI-class metalloproteinase atroxlysin-Ia from the venom of Bothrops atrox has dermonecrotic activity. Its function is supported by the disruption of the extracellular matrix, matrix metalloproteinases induction and severe damage to skin and subcutaneous tissues. This complicates the healing of wounds and results in a considerable cosmetic-functional defect [29].

Apoptosis induced by L-amino-acid oxidase from Bothrops alternatus snake venom: Involvement of mitochondria and caspase activation. Besides cytotoxic, it is reported to be an antimicrobial reducing local infections. These indicate the multifunctionality of the venom enzymes and their possible applications in therapy [30].

Conclusions. Venom of snakes is a complex biological mixture that contains enzymes, toxic proteins and low molecular weight compounds that induce local and systemic pathophysiological effects. Its constituents do harm to the cell membrane, induce inflammation, haemorrhaging and hemostasis disorders, neurotoxity disease and tissue necrosis. An exclusive place in the genesis of the clinical picture occupies phospholipase A2, metalloproteinases and serine proteases that act together, activating many "pathologic" cascades at once. Several venom enzymes, in addition to their toxicity, also show anticoagulant, antimicrobial or immunodulatory properties providing a future destination for their therapeutic use as well. The severity and type of effects are dominated by the composition, dose, route of entry and duration of action of venoms. Mechanism of action of single toxins is essential for the development of efficient therapy and also to discover new pharmacological agents.

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