SNAKE VENOM TOXINS

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Snakes are limbless reptiles, known to men since the days of antiquities. These small creatures have been a focus of attention in human history. They have enjoyed various positions in different parts of the world. They have been both revered and reviled. They have been prayed by some communities and hatred in others. The attention sought by these animals is probably due to the production of venom. Venom is a form of toxin secreted to cause harm to another animal in defense or to hunt a prey[1].

Venom is a specialized secretion produced by venomous glands. Snake venom is produced by mandibular glands, located below the eye. It is delivered to the victim through channeled or grooved teeth, called fangs. Snake venoms contain a variety of peptide toxins, including proteases, which hydrolyze protein peptide bonds, nucleases, which hydrolyze the phosphodiester bonds of DNA, phospholipases, which hydrolyze phosphodiester bonds and neurotoxins, which disable signaling in the nervous system. All this is done by complex mixture of enzymes, peptides, carbohydrates, minerals and proteins of low molecular mass with specific chemical and biological activities. Various peptides and protein fractions display activities as cytotoxins, cardiotoxins, hemotoxins, neurotoxins etc.[2,3].

Venoms adapt to their environment and victims and accordingly evolve to become maximally efficient on a predator's particular prey. Consequently, venoms become specialized to an animal's standard diet. The potency of different venoms varies; lethal venoms are often characterized by the median lethal dose (LD50, LD50, or LD-50), expressed in terms of mass fraction (e.g., milligrams of toxin per kilogram of body mass), that will kill 50% of the target of a specified type (e.g., laboratory mice)[4].

A variety of pathophysiological effects produced by envenomation include, local tissue damage and/or systemic effects, including pain, swelling, tissue necrosis, low blood pressure, convulsions, hemorrhage, respiratory paralysis, kidney failure, coma and death[5,6]. The major types of biomolecules found in snake venom are proteins of both enzymatic as well as non enzymaticnature.The most potent toxins of snake venom, responsible for causing severe pathophysiological effects are neurotoxins[7], cytotoxins[8] , phospholipase A_2 (PLA_2)[9] and Zn^{2+}-dependent metalloproteinases[10].

Snake venom cytotoxins are basic proteins. These toxins may have direct lytic factors, cardiotoxins, cobramines, cytolysins, and membranotoxins[11]. It is widely accepted that most pathological activities of cytotoxins are based on their ability to bind to cell membranes leading to alterations in the organization and function of lipid bilayers[12]. Cytotoxin-mediated toxicity include modulating the activity of membrane-bound enzymes, depolarizing excitable membranes of heart cells and of neurons, inhibiting platelet aggregation, inducing hemolysis and cytotoxicity, and bringing about cardiac arrest[13].

A variety of pit viper venoms contain fibrinolytic activity. However, the level of this proteolytic activity is highly variable even within a particular genus of snakes. The proteolytic degradation of capillary membrane proteins and the leakage of blood components from the vasculature into surrounding tissues underlie the hemorrhagic activity of the venom. The hemorrhagic potency of venoms causing profuse hemorrhage, blood coagulation, and the inactivation/activation of complement proteins differs from specie to specie[14]. The pathophysiological spectrum induced by hemorrhagic venom also includes the formation of platelet plugs in blood vessels, the swelling and disruption of endothelial cells in capillaries, profuse hemorrhage, blood coagulation, fibrinolytic activity, prothrombin activation etc[15].

Variation in the action is attributed to structural differences of these enzymes located at interconnecting loop of the catalytic cleft[16]. Clinically, there are two potent anti-sera that have been developed and tested in clinical trials for treating snakebite victims due to envenomation by Echis and Naja snakes. These two anti-venoms can stop the profuse hemorrhage,

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neutralized by immunodepletion by certain anti-sera used for treating snakebite victims[17].

Clinically, snake envenomation is prevalent and contributes to a high mortality rate in developing countries. Moreover, it is disappointing that the lack of sufficient anti-venom supplies and clinics has not been addressed in developing countries. Hence, it is imperative that more funding and research is dedicated towards finding more efficient anti-venom and alternative treatments in order to significantly decrease the number of deaths due to snakebites.

On the other hand, many of these proteins possess pharmacologically relevant properties that can be used for treating a variety of human disorders and conditions including hemophilia, deep vein thrombosis, cancer, autoimmune disorders, and neurodegenerative diseases. For instance, cobra venom cytotoxins are widely studied for their anti-cancer properties. Moreover, research studies on the molecular mechanisms that modulate PLA2-associated activities may be useful for designing drugs to suppress over-activity of endogenous PLA2 associated with various inflammations and autoimmune disorders[18]. Finally, snake venom proteins are modulated as drugs for treating diseases involving abnormal blood clot formation and for reversing brain pathology as observed for some neurodegenerative disorders. In summary, there is a huge pharmacological potential found in snake venom that needs to be exploited by pharmaceutical companies, leading to the development of new therapeutic agents for the treatment of different human diseases and disorders.

It has been estimated worldwide, that approximately 2,500,000 human beings suffer from snakebites per year which result in over 125,000 deaths. Most lethal snakebites predominantly occur in Africa and Asia and are caused by approximately 410 venomous species of snakes. Clinically, administering anti-venom to the affected patient within 2 hours, efficiently reverses many of the detrimental systemic effects caused by snake venom including nephrotoxicity, myotoxicity, and necrosis. Depending on the composition of snake venom, patients may be cotreated with atropine followed by acetylcholinesterase inhibitors in case that neurotoxicity is induced by muscarinic receptor inhibitors. Following anti-venomtreatment, the patient is hydrated, and necrotic tissue can be removed by debridement[19]. However, it is widely recognized by many clinicians and toxinologists that administering broad-spectrum antisera may not be the most efficient way for treating snakebite victims due to the highly diverse pharmacological properties of snake venom across snake species [20]. Therefore, generating new anti-venom based on purified recombinant toxins, geographic location of snake species that produce the envenomation, and severity of pathology may be the best alternative for treating snake bite victims. On the other hand, limited research and limited federal-supported funding for antivenom research has hampered the availability and diversity of efficient anti-venom.

References

1. Kordiš D.; Gubenšek F. (2000). "Adaptive evolution of animal toxin multigene families". Gene. 261: 4352. doi:10.1016/s0378-1119(00)00490-x.
2. SK Pal, A Gomes, SC Dasgupta, A Gomes Snake venom as therapeutic agents: from toxin to drug development. Indian J ExpBiol, 40 (2002), pp. 1353-1358
3. LA Calderon, JC Sobrinho, KD Zaqueo, AA de Moura, AN Grabner, MV Mazzi, *et al.* Antitumoral activity of snake venom proteins: new trends in cancer therapy. Biomed Res Int (2014), 10.1155/2014/203639.
4. Ligabue-Braun R.; Verli H.; Carlini C. R. (2012). "Venomous mammals: a review". Toxicon. 59: 680695. doi:10.1016/j.toxicon.2012.02.012.
5. León G, Sánchez L, Hernández A, Villalta M, Herrera M, et al. (2011) Immune response towards snake venoms. Inflamm Allergy Drug Targets 10: 381-398.
6. Dubovskii PV, Konshina AG, Efremov RG (2013) Cobra cardiotoxins: membrane interactions and pharmacological potential. Curr Med Chem 21: 270-287.
7. Nirthanan S, Gwee MC (2004) Three-finger alpha-neurotoxins and the nicotinic acetylcholine receptor, forty years on. J PharmacolSci 94: 1-17.
8. Konshina AG, Boldyrev IA, Utkin YN, Omel'kov AV, Efremov RG (2011) Snake cytotoxins bind to membranes via interactions with phosphatidylserine head groups of lipids. PLoS One 6: e19064.
9. Chaisakul, J Parkington HC, Isbister GK, Konstantakopoulos N, Hodgson WC (2013) Differential myotoxic and cytotoxic activities of pre-synaptic neurotoxins from Papuan taipan (Oxyuranusscutellatus) and IrianJayan death adder (Acanthophisrugosus) venoms. Basic ClinPharmacolToxicol 112: 325-334.
10. Markland FS Jr, Swenson S (2013) Snake venom metalloproteinases. Toxicon 62: 3-18.
11. Rees B, Bilwes A (1993) Three-dimensional structures of neurotoxins and cardiotoxins. Chem Res Toxicol 6: 385-406.
12. Kumar TK, Jayaraman G, Lee CS, Arunkumar AI, Sivaraman T, et al. (1997) Snake venom cardiotoxins-structure, dynamics, function and folding. J BiomolStructDyn 15: 431-463.
13. Harvey AL (1990) Cytolytic toxins. Handook of Toxicology. Marcel Dekker Inc, New York, USA, 66.

14. Castro EN Lomonte B, del Carmen Gutiérrez M, Alagón A, Gutiérrez JM (2013) Intraspecies variation in the venom of the rattlesnake Crotalussimus from Mexico: different expression of crotoxin results in highly variable
15. Berger M, Pinto AF, Guimaraes JA, (2008) Purification and functional characterization of bothrojaractivase, a prothrombin-activating metalloproteinase isolated from Bothropsjararaca snake venom. Toxicon 51: 488-501.
16. Fox JW, Serrano SM (2008) Insights into and speculations about snake venom metalloproteinase (SVMP) synthesis, folding and disulfide bond formation and their contribution to venom complexity. FEBS J 275: 3016-3030.
17. Calvete JJ, Cid P, Sanz L, Segura A, Villalta M, et al. (2010) Antivenomic assessment of the immunological reactivity of EchiTAb-Plus-ICP, an antivenom for the treatment of snakebite envenoming in sub-Saharan Africa. Am J Trop Med Hyg 82: 1194-1201.
18. Wu M, Ming W, Tang Y, Zhou S, Kong T, et al. (2013) The anticancer effect of cytotoxin 1 from Najaatra Cantor venom is mediated by a lysosomal cell death pathway involving lysosomal membrane permeabilization and cathepsin B release. Am J Chin Med 41: 643-663.
19. Cruz LS, Vargas R, Lopes AA (2009) Snakebite envenomation and death in the developing world. Ethn Dis 19: S1-42-6.
20. Castro EN Lomonte B, del Carmen Gutiérrez M, Alagón A, Gutiérrez JM (2013) Intraspecies variation in the venom of the rattlesnake Crotalussimus from Mexico: different expression of crotoxin results in highly variable toxicity in the venoms of three subspecies. J Proteomics 87: 103-121.