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Pharmacology of Spider Venom Toxin

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Because of their physical characteristics, predatory tendencies, secretive habits, and perceived potential for harm, spiders have long occupied a unique place in popular mythology and folklore. However, only a small number of species provide a real medical concern, despite their enormous biological and ecological diversity (around 40,000 species have been described and likely over 100,000 have not yet been). Based on the location of their chelicera, spiders are classified into two main groups. With the exception of Australian species of the genus Hadronyche (Atrax), many large specimens of the more primitive orthognath spiders (mygalomorphs) do not correlate with high venom toxicity. These spiders display a very aggressive behavior, coupled with a venom which is highly toxic for humans, and have caused at least 14 recorded deaths. Other dangerous mygalomorphs include species in the genus *Trechona* (Dipluridae) and *Harpactirella* (Barychelidae). In the family Theraphosidae, whose members have become wildly popular as pets, the dangerous character of the venom is mostly limited to hearsay, and cases of severe envenomation are usually unsubstantiated. No deaths have been officially recorded to date, although several species are reported to provoke severe envenomation symptoms. A complex mixture of mostly enzymatic and non-enzymatic protein and peptide poisons makes up spider venom. Furthermore, there are free amino acids, monoamines, polyamine neurotoxins, and inorganic salts (Min *et al.*, 2013). Prey acquisition and defense are the venom's primary roles. Numerous pharmacological effects, such as edema, hemorrhage, dermo/myonecrosis, hemolysis, inflammation, neurotoxicity, cytotoxicity, and changes in platelet and coagulation function, have been linked to spider venom (Devaraja *et al.*, 2011). Several neurotoxic, cytotoxic, antimicrobial, anti-insecticidal, anti-arrhythmic, antiparasitic, trypsin inhibitory peptides and enzymes such as hyaluronidase, proteases, phospholipase D and sphingomyelinase D have been isolated and characterized from various spider venoms. Spider venom peptide toxins have been extensively studied through proteomic and transcriptomic approaches.

Pharmacological properties of spider venom

Despite the fact that the spider bite was an unintentional incident, the sufferer of envenomation experiences a number of pharmacological effects. There are two main stages of envenomation: the first starts minutes after the bite, and the second occurs when the poisons go away, usually several hours later. The majority of spiders don't have any deadly effects; just a tiny percentage of them can kill people (Lung & Mallory, 2000). The pathophysiology appears to involve a complex series of events that depends on the combined and perhaps synergistic action of the venom toxins (Nagaraju *et al.*, 2006). The

pathophysiology includes ‘‘Local toxicity’’ (edema, hemor rhage, myo/dermonecrosis) and ‘‘Systemic toxicity’’ (neuro toxicity, cytotoxicity, cardiotoxicity, myotoxicity, interference in coagulation [pro/anti] and platelet function). The spider bite may also produce considerable local tissue necrosis with scar formation and ulcers that may require surgical repair. The victims may suffer from intravascular hemolysis, dissemi nated coagulation and acute renal failure leading to death.

Local toxicity : Early signs of a spider bite include local toxicity or alterations that occur within 6 to 8 minutes, however they can start as early as 30 minutes. It takes more than 30 minutes for the venom of Australian funnel-web spiders and loxosceles to produce local effects. Pain, redness, swelling, diaphoresis, and itching have all been reported to be symptoms of Australian spiders, which are members of the genera *Latrodectus, Steatoda, Sparassidae*, *Lycosidae*, *Lamponidae*, and *Mygalomorphae* (Isbister & White 2004). The spiders of the genus *Hippasa* (*H. partita*, *H. agelenoides* and *H. lycosina*) belongs to the Western Ghats of Karnataka, India, found to cause severe edema, itching, acute pain and sometimes hemorrhage following tissue necrosis in farm and plantation workers (Nagaraju *et al*., 2006). In general, a small reddish wheal forms at the bitten region along with swelling that results in edema, echymoses (pinpoint red spots on the skin), hemorrhage and dermo/myonecrosis that are usually visible within minutes of the bite. The local area of the bite may become devascularized with features of necrosis predisposing to onset of gangrenous changes.

Edema : Interstitial fluid levels often fall within the range of homeostasis. Edema may result from either increased fluid secretion into the interstitium or poor fluid clearance. Edema, which was historically referred to as hydropsy or dropsy, is the accumulation of interstitial fluid in any organ or tissue. Osmotic and hydrostatic pressures, which work in opposing directions across the semipermeable blood capillary walls, must be balanced for interstitial fluid to be generated.

Hemorrhage : The medical term for bleeding is hemorrhage. Although a hemorrhage technically refers to blood escaping into extravascular space due to damage to the blood wall's microvessels, the term is commonly used to refer to significant bleeding. The majority of the bleeding caused by venoms is caused by zinc-dependent metalloproteases of the "metzincin" family of enzymes. Metalloproteases typically cause bleeding by breaking down the endothelium's extracellular matrix components. The majority of spider venom, including that of *Loxosceles* species, *H. partita*, and pure "Partitagin" from *H. partita* spiders, has been shown to induce bleeding.

Dermo-/myo-necrosis : The loss of integrity of extracellular matrix molecules due to the degradation of extracellular matrix degrading venom enzymes is an important process in the development of dermo-/myo-necrosis. In addition to hemorrhagic metallo proteases, hyaluronidases and myotoxic phospholipases, sphingomyelinase D are also implicated in inducing dermo-/ myo-necrosis. The whole venom of *L. intermedia* and the purified enzymes such as sphingomyelinase D and phospholipase D from *Loxosceles reclusa* were found to cause dermonecrosis.

Systemic toxicity

Systemic toxicity results from the circulating blood's dispersion of systemic poisons into their specific targets. The concentration, effectiveness, and rate at which systemic poisons diffuse into the bloodstream from the bite site determine the systemic toxicity. Neurotoxicity, cytotoxicity, myotoxicity, cardiotoxicity, impact on hemostasis, hemolysis, and renal failure are all examples of systemic toxicity.

Neurotoxicity : In fact, a wide variety of neurotoxins can be found in spider venom. Since paralyzing the victim is the main function of spider venom, it contains a wide range of poisons that have an impact on the neurological system. The majority of spider venom neurotoxins that have been identified so far are either acyl polyamines or proteins/peptides. It has been discovered that they have a range of effects on the nervous system. Consequently,

it seems that the bulk of spider venom neurotoxins target the pre-synaptic membrane proteins involved in neurotransmitter release, neuronal receptors, or neuronal ion channels.

Cytotoxicity : It has been discovered that several cell lines are cytotoxically affected by spider venom. Human neutrophils were cytotoxically affected by loxosceles recluse venom, which at greater concentrations prevented complement-induced neutrophil chemotaxis. According to Luciano *et al*. (2004), envenomation by *Loxosceles* spiders causes nephrotoxicity, where the toxins attach to the kidney cells' basement membranes, tubule cells, and glomerular membrane. This causes tubule cell damage, endothelial cell cytotoxicity, hyalinosis, and proteinuria.

Myotoxicity : Myotoxicity is the term used to describe the harm that matrix metalloproteases, phospholipase A2, and the neurotoxic peptides found in spider venom cause to skeletal myofibrils. A myotoxic peptide Covalitoxin-I was isolated from the venom of the Singapore tarantula *Corecnemius validus* that caused necrosis of mouse skeletal muscle.

Therapeutic applications of spider toxins

Toxins from a variety of venomous creatures, including snakes, leeches, cone snails, lizards, and honey, are currently becoming increasingly significant because of their numerous biological and biotechnological uses as diagnostic and therapeutic agents. For example, the authorized medications for the treatment of hypertension, anticoagulation during surgery, and type 2 diabetes are captropril from pit vipers, bivalirudin from leeches, and exenatide from lizards, respectively. However, none of the toxins found in spider venom are now available as licensed medications. However, researchers were able to investigate biotechnological applications of spider venom components in a remarkable way because to the advent of new molecular biology tools. Several antibacterial peptides were reported from various spider venoms, the antibacterial peptide from the venom of the *Cupiennius salei* spider acts channel forming toxins within the bacteria wall. Spider venom hyaluronidases could be used in identifying hyaluronidase inhibitors. This could further help in the development of numerous therapeutic agents such as contraceptives, anti-tumor, anti-microbial, anti-venom, anti-wrinkle, anti-aging and inflammation suppressors.

Conclusion

The diverse range of real pharmacologically active enzymatic and non-enzymatic poisons is best exemplified by spider venom. These poisons are used for both defense and prey acquisition. A spider bite is an unintentional incident that can result in serious health issues. Humans and domesticated animals are the most common victims of spider bites. Necrotic wounds and systemic poisoning are uncommon symptoms, even though 98–99% of bites are benign. Even though the spider venom contained a number of enzymatic poisons, only the pharmacology of spingomyelinase, phospholipase, proteases, and hyaluronidases has been determined thus far. Hence, the spider venom toxin research became one of the fascinating fields. However, there are several drawbacks associated with spider venom research. As spider is a tiny organism and available in a specific season, getting venom in sufficient quantity is a tedious job.

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