SNAKE VENOM HEMORRHAGINS

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Due to the complexity of most snake venoms, different biological effects may be observed after envenomation. Bleeding is common in crotalinae envenomation and is likely to result from one or more factors in the venom. The main factors are hemorrhagic toxins and the others are components which produce a non clotting effect. The hemorrhagic principles destroy the basement membrane of the capillary vessels. However, damage of the endothelial cells can not be ruled out. These causes affecting the stability of the vessel wall allow the red blood cells to escape from the capillaries. A great number of metalloproteases have been isolated from different snake venoms and many of them were characterized as hemorrhagins. It is noteworthy that both hemorrhagic and nonhemorrhagic metalloproteases of snake venoms can be similar in proteolytic specificity. Some times two metalloproteases isolated from the same venom can hydrolyze the same substrates, but one is hemorrhagic and the other is nonhemorrhagic or this activity is only observed in very high doses compared to the hemorrhagic one. For instance the hemorrhagic factor HF_2 and bothropasin isolated from the venom of *B. jararaca* hydrolyze casein, B-chain of insulin, fibrinogen, and have similar molecular weights 49,100 and 48,000, respectively. However, HF_2 is 50 times more hemorrhagic than bothropasin. The hemorrhagins degrade fibrinogen, acting mostly on A and B β chain like some other snake metalloproteases. The cleavage of insulin B-chain by venom hemorrhagic proteases is very similar to the cleavage of other venom metalloproteases nonhemorrhagic. Both show a preference to cleave on N-terminal side of Leu bonds. However, all snake venom hemorrhagins are distinguished from the other metalloproteases by their limited substrate specificity: the action on basement membrane of the capillary vessels. It was demonstrated with hemorragic toxins from *C. atrox* that they degrade the components of the extracellular matrix of the capillary vessels, such as type IV collagen, laminin, and nidogen but not fibronectin[2].

Snake venoms from Asia and North America have been exhaustively studied and many hemorrhagic principles were isolated from them. As for the Latin Ame-

rican snakes, hemorrhagins were isolated only from some *Bothrops* species and from *Lachesis muta muta*. The hemorrhagins isolated from venoms of *Bothrops* genus are structuraly similar proteins. They behave very similarly to the homologous antigens on immunoprecipitation, C' fixation and neutralization reactions[1,3] It was also found that the *Bothrops* hemorrhagins have epitopes similar to the hemorrhagins of North American *Crotalus* and to the Asian *Trimeresurus* and *Agkistrodon* species. The *Bothrops* hemorrhagins have also few epitopes in common with venoms of *Vipera* snakes. Although the antisera to the *Bothrops* hemorrhagic proteins do not cross react with these venoms, they neutralize partially their hemorrhagic activity, possible by steric hindrance of the active hemorrhagic center or by some allosteric modification due to the combination of the immunoglobulins with the corresponding epitope(s).[4]

Hemorrhagins of same molecular weight isolated from venoms of different snake genus show a great structural homology.[5] On the other hand it was found that hemorrhagic and nonhemorrhagic metalloproteases isolated from the same snake venom have about 75% sequence homology.[6,7] The difference of the hemorrhagic and nonhemorrhagic protein is located at the middle position 51-130 of the molecule. However, the determining residues positions that are responsible for the binding with the basement membrane to induce hemorrhage were not yet determined.

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