LOCAL PATHOLOGICAL EFFECTS INDUCED BY *BOTHROPS* SNAKE VENOMS

José Maria Gutierrez, Instituto Clodomiro Picado, Facultad de Microbiologia, Universidad de Costa Rica, San José, Costa Rica.

Envenomations caused by snakes of the genus *Bothrops* induce conspicuous local tissue damage. This effect, which appears soon after venom injection, is characterized by myonecrosis, hemorrhage and edema. Muscle necrosis is due to (a) the action of myotoxins, some of which have phospholipase A_2 structure. Myotoxins affect the integrity of skeletal muscle plasma membrane by a mechanism not directly related to phospholipid hydrolysis. (b) The ischemia that develops in muscle tissue as a consequence of drastic vasculature damage, i.e. hemorrhage and arterial lesions. A portion of necrotic muscle regenerates after venom induced damage. However, in many cases muscle regeneration is poor, mainly due to the alteration of muscle microvasculature.

Hemorrhage is caused by the action of metalloproteases which probably degrade collagen and other components of the basal lamina of capillary vessels. As a consequence, capillaries are disrupted and hemorrhage occurs. It is also possible that hemorrhagic toxins affect directly the endothelial cells of capillaries, although this has not been clearly established. There is a conspicuous immunologic cross-reactivity of hemorrhagic toxins in *Bothrops* venoms, and antivenoms usually have high neutralizing ability against these toxins when tested by the traditional preincubation assay. However, when antivenoms are administered after venom injection, neutralization of hemorrhage and myonecrosis is only partial, probably due to the rapid development of these effects once venom is injected.

Local edema is a typical manifestation of envenomations by *Bothrops* snakes. It is probably caused by a combination of elements such as: direct effect of venom on vessels and release of endogenous mediators like histamine, kinins and prostaglandins due to the action of venom components on mast cells, kininogens and phospholipids, respectively. In some cases, edema is responsible for elevation of interstitial hydrostatic pressure in muscle compartments, which might re-

sult in a compartmental syndrome. Antivenoms are usually of low efficacy in neutralizing edema. Thus, new pharmacological approaches must be introduced to deal with this relevant effect.

Besides their action on muscle cells and microvasculature, *Bothrops* venoms also affect arteries, inducing thrombosis and damage to the arterial walls. Arterial damage, in turn, causes ischemia and further muscle necrosis. In addition, these venoms affect intramuscular nerves. This effect may be relevant for muscle regeneration, since intact innervation is a basic requirement for skeletal muscle regeneration.

Acknowledgements:Parts of this research have been supported by University of Costa Rica, International Foundation for Science and the Third World Academy of Sciences.