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SHORT EDITORIAL

Understanding the Bothrops Moojeni Venom: A Justified Challenge

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Short Editorial referring to the article: Bothrops Moojeni Snake Venom: A Source of Potential Therapeutic Agents Against Hemostatic Disorders

Snakes, scorpions, spiders, wasps, and fish have evolved independent venom systems with complex mixtures in their chemical arsenals. Envenomation after a snakebite is a neglected public health issue responsible for substantial illness and death in impoverished populations living in rural and tropical Africa, Asia, Oceania, and Latin America.

Considering the elevated number of accidents and high morbidity and mortality rates associated with snakebite envenoming, the World Health Organization has reclassified this disease as a category A neglected disease. In Latin America, snakes of the *Bothrops* genus are the main responsible for snakebites in humans, causing inflammatory and hemostatic alterations whose pathophysiology is a neglected issue in the toxinology field.[1]

In this issue of the *International Journal of Cardiovascular Sciences*, Natália Barreira Silva et al. present a systematic review conducted according to the PRISMA protocol using the terms "Bothrops" and "hemostasis" of scientific articles published in the last 20 years.[2] The authors describe 23 proteins isolated from *Bothrops moojeni (B. moojeni)* venom that affect hemostasis and their pharmacological and clinical potential. These proteins have already been characterized regarding their effects on hemostasis and possible applications in the diagnosis and treatment of hemostatic disorders. *B. moojeni* venom is mainly composed of snake venom metalloproteases (SVMPs) (36.5–39.8%), snake venom serine proteases (SVSPs) (14.7–19.8%), phospholipase A_2 (PLA_2) (11.5–17.1%), L-amino acid oxidases (LAAOs) (4.2–5.2%), and lectins (2.4–3.1%). Among the less abundant toxins are vascular endothelial growth factors (VEGFs), bradykinin-potentiating peptides (BPPs), cysteine-rich secreting protein (CRISP), 5'-nucleotidases, and hyaluronidases, which, together, represent less than 15% of the total protein content of the venom.

Hemostasis is a complex process that involves interactions between different components, such as platelets, blood proteins, and endothelial cells. Despite the number of *B. moojeni venom* proteins known to interfere with the various events of hemostasis, little is known about their mechanisms of action, and there are still several less-known protein classes.

According to the references cited in this review, many SVMPs isolated from B. moojeni venom have been characterized for their effect on hemostasis, such as BmooFIBMP-I, BmooMPα-I, BmooMPα-II, BthMP, and BmooMP-I, belonging to the P-I class, and BmooPAi, Moojenactivase and Moojenin belonging to the P-III class. Divergent activities of some toxins on hemostasis reflect the complexity of this venom. While BmooMPα-I and BthMP exert fibrinolytic and anticoagulant activities in vivo moojenactivase shows procoagulant activity in vitro (with the activation of factors II and X) and non-fibrinolytic activity. Also, Batroxobin (Defibrase®) and BmooSP serine proteases present fibrinogenolytic and procoagulant activity in vitro but anticoagulant action in vivo. On the other hand, BmooPLA inhibits aggregation, and BmooTX-I activates aggregation, whereas both MjTX-III and MjTX-extend blood clotting time and neutralize heparin.

The mechanism of action of hemorrhagic SVMPs is a challenging area of research. Despite structural similarities, the hemorrhagic potential of P-I, P-II, and P-III SVMPs differs between them, and the basis of this functional heterogeneity is unknown. Also, some P-III SVMPs exert a procoagulant effect, by activating factors II and X of the coagulation cascade.[3]

Keywords

Snakes; Bothrops; Venoms.

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Venom-induced tissue damage to cellular and extracellular matrix targets involves multiple simultaneous processes. In addition, inflammatory processes are amplified, and toxins, endogenous mediators, and tissue-derived molecules that exert biological actions and synergisms between toxins are released.

Inflammatory responses and coagulation disorders are considered hallmark mechanisms of local and systemic effects of Bothrops snakebites.[1] Crosstalk is responsible for potentiating both inflammatory and hemostatic alterations and enhancing prothrombotic conditions associated with thrombotic microangiopathy. Tissue ischemia is a recent issue in toxinology. Therefore, studies on the crosstalk between hemostasis/inflammation and thromboinflammatory events should be encouraged to identify new mechanisms and to understand their role in the pathophysiology of envenomation. The search for thromboinflammatory markers with predictive or prognostic roles could contribute to improve clinical conditions.

In a new era of biological therapeutics, venom peptides are an interesting alternative strategy for target engagement, with greater stability than antibodies or human peptides. Therefore, animal venoms represent an invaluable source of scientific discoveries, to the development not only of new therapeutic agonists but also of useful tools to identify endogenous and exogenous molecules that act on hemostasis.[4] In this context, even understanding the responses of mammalian organisms to injuries induced by snake venoms can be useful to unravel the pathophysiology of envenomation and the mammalian physiology.

Classic examples of endogenous mediators directly released by Bothrops venom toxins include the nonapeptide bradykinin, discovered in 1949,[5] and captopril,[6] the first active-site-directed inhibitor of angiotensin-converting enzyme. The latter was developed based on studies on the *Bothrops jararaca* (*B. jararaca*) snake venom, and is used worldwide to treat human hypertension. The activation of the hepatocyte growth factor (HGF)/c-met pathway is another example of an endogenous mediator indirectly generated by thrombin formation induced by accidental envenoming by venoms from most Viperidae. The HGF/c-met pathway consists of two plasma proteins, the HGF activator (HGFA) and its substrate proHGF, which act on the cell membrane's mesenchymal–epithelial transition receptor (c-met). This pathway is important to tissue architecture during embryonic development and maintenance of homeostasis in adult tissue, contributing to the repair of injured epithelial and nonepithelial organs and blood vessels via mitogenic, angiogenic, antiapoptotic, and anti-inflammatory signals.[7] Thrombin is the physiological activator of the HGF/c-met pathway, cleaving proHGF activator (proHGFA) at the Arg_{407}-Ile_{408} bond, and active HGFA cleaves proHGF to active HGF, which binds with high affinity to the c-met receptor.[8] The generation of plasma thrombin and proinflammatory cytokines in tissues are powerful stimuli for activation and positive regulation of HGF expression, respectively. Experimental envenomation of rats with *B. jararaca* venom activated the HGF/c-met pathway, significantly elevating HGF plasma levels.[9] Serum concentrations of HGF have been proposed as diagnostic and prognostic biomarkers in patients with overt disseminated intravascular coagulopathy.[10]

Furthermore, the inflammatory process caused by Bothrops venoms involves leukocyte infiltration—mainly polymorphonuclear and/or mononuclear cells at the site of injury—and other resident cells that produce and release cytokines in response to the Bothrops snake venom.[11] Bothrops venom toxins are also capable of inducing cytokine synthesis. For example, the cytokine release of tumor necrosis factor-alpha (TNF-α) and interleukins 1β (IL-1β) and 10 (IL-10) in the kidneys can be increased by the action of Asp-$_{49}$ PLA_2 and Lys-$_{49}$ PLA_2 from B. pauloensis venom.[12] Several proinflammatory cytokines, such as IL-1, IL-6, TNF-α, IL-1α, and IL-1β, are positive regulators of HGF expression and production.[13] Moreover, HGF and c-met have remarkable potential as diagnostic and prognostic biomarkers of disseminated intravascular coagulopathy induced by snake venoms. HGF is produced in response to tissue injury and contributes to organ restoration. This explains why HGF supplementation stimulates the regeneration of injured tissues, specifically in the kidney, liver, skin, cartilage, renal tubular cells, and neurons.[14] Advances in the understanding of the coagulation/inflammation interface and the complex pathology triggered by snake venoms and toxins may enable the discovery of new therapeutic targets and procedures and thereby reduce mortality and morbidity from envenomation. It is expected that this review will stimulate innovative research in the field.

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