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Review

Lonomia obliqua venom: *In vivo* effects and molecular aspects associated with the hemorrhagic syndrome

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ABSTRACT

Caterpillar envenomation has been an emergent health issue. *Lonomia obliqua* is a medically important animal that causes a hemorrhagic syndrome that can progress to acute renal failure, intracranial hemorrhage and death. In the past few years the molecular characterization of *L. obliqua* venom in addition to experimental models has provided fundamental information to the understanding of the envenomation syndrome. Herein studies from several authors which characterized the complex toxic-pharmacological actions of whole venom are reviewed.

1. Introduction

Accidental contact with some lepidopteran caterpillars can inflict serious human injuries ranging from simple skin irritation to serious burns, allergic reactions, renal failure and hemorrhagic disturbances (Diaz, 2005). Like other venomous animals, such as snakes and spiders, these caterpillars produce a variety of toxic components that affect the vascular system, blood coagulation, fibrinolysis and platelet function (Arocha-Piñango et al., 2000). However, different from snakes and spiders, that use their venoms to immobilize and digest the prey, the caterpillar venomous components are useful for defense against predators.

From the medically important Saturniidae family, *Lonomia* genus has been attributed to cause human envenomations since late 1960s in Venezuela (Arocha-Piñango and Larysse, 1969). In Southern Brazil, *Lonomia obliqua* (Fig. 1a) caterpillar is becoming the most important venomous animal responsible for severe injuries, hemorrhagic disorders and often fatal outcome since the 1980s (Duarte et al., 1990). For instance, in the State of Rio Grande do Sul, located in this Brazilian region, more than a thousand accidents have been registered in the 1997 to 2005 period (Abella et al., 2006). In fact, based in the data for the year 2008, the Brazilian Ministry of Health registered an incidence of 8 lepidopteran envenomations per 100,000 inhabitants in Southern Brazil (SVS, 2009). Actually, this numbers are greatly underestimated due to the fact that most accidents are occurring in distant rural areas, where the cases are poorly reported. The emergent importance of *L. obliqua* accidents seems to be consequence to the extensive deforestation of rural areas and replacement of the native forest by fruit tree plantation, a rich source of food for this lepidopteran. The *L. obliqua* has gregarious habits, and this characteristic complicate the patient prognosis, since the accidents usually involve the contact of the victim with a caterpillar colony containing dozens or hundreds of caterpillars lying on the surface of tree trunks.

L. obliqua is venomous only in the larval stages (1st to 6th instars), when the body of the insect is covered by

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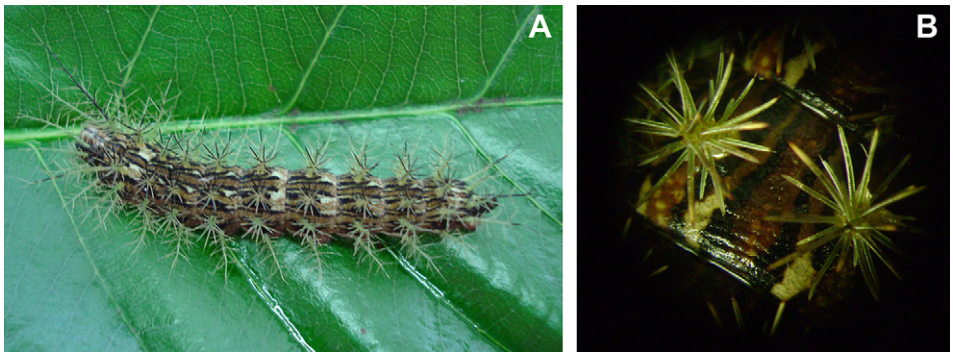

Fig. 1. The *Lonomia obliqua* caterpillar. A. *L. obliqua* (6th instar). B. Detail of *L. obliqua* bristles.

chitinous bristles (Fig. 1b). These structures are hard and spiny evaginations of the cuticle underneath. Contrarily to other venomous animals, there is no specialized venomous gland in *L. obliqua* and the venom is produced by a secretory epithelium localized under the cuticle (Veiga et al., 2001). The bristles have a hollow canal by which the venom is injected in the victim. The accident occurs when the whole animal is crushed by the victim; the insect's chitinous bristles are broken and the venomous secretions penetrate the human skin reaching blood circulation (Veiga et al., 2001).

In this review, we focused in studies that provided significant contributions to the comprehension of the biological effects of the whole venom in experimental models. In fact, these reports are responsible for identification and characterization of venom mechanisms capable of reproducing some of the main physiopathological aspects of the clinical envenomation.

2. Clinical aspects of human envenomation

Clinical symptoms of *L. obliqua* envenomation include local pain and inflammatory reaction, which starts immediately after contact; systemic reactions such as headache, fever, vomiting and asthenia, which appear a few hours after exposure; and bleeding diathesis characterized by hematomas and ecchymosis, hematuria, pulmonary and intracerebral hemorrhage and acute renal failure (Burdmann et al., 1996; Kowacs et al., 2006; Garcia and Danni-Oliveira, 2007).

Poisoned patients present a severe prolongation of the coagulation parameters such as prothrombin time (PT) and partial activated thromboplastin time (aPTT). Laboratory findings include a decrease in plasma levels of fibrinogen, factors V and XIII, pre-kallikrein, plasminogen, protein C and α2-antiplasmin, and an increase in the levels of thrombin-antithrombin complex (TAT), fragment $1+2$ from prothrombin activation (F1.2) and D-dimers. No alterations in von Willebrand Factor, factors X and II levels were found (Kelen et al., 1995; Zannin et al., 2003). Taken together, these clinical data indicate that a significant amount of intravascular thrombin is generated and the fibrinolytic system is activated in *L. obliqua* envenomation. The activation of blood coagulation and fibrinolysis causes the consumption of plasmatic factors leading to a consumption coagulopathy characteristic of this type of envenomation.

Despite this intense consumption coagulopathy, the platelet number appears to be diminished only in the most severe cases, been normal in mild ones (Zannin et al., 2003). However, the platelet function of these patients during envenomation has not been evaluated. Considering that platelets participate in several steps of the hemostatic process, including the amplification and propagation phases of the blood coagulation (Monroe and Hoffman, 2006; Hoffman and Monroe, 2001), these elements probably make a decisive contribution to the appearance of hemorrhagic syndrome during envenomation. Analogously, patients envenomed by *Bothrops jararaca* snakes presented a significant impairment of the platelet function that has been associated with the bleeding disorders observed after envenomation (Sano-Martins et al., 1997).

Besides the bleeding disorders, *Lonomia*-envenomed patients also develop renal problems. Hematuria is observed in most patients and may evolve to acute renal failure (Burdmann et al., 1996). A few histological reports of renal tissue of envenomed patients are consistent with tubular necrosis (Burdmann et al., 1996; Fan et al., 1998), but the pathogenesis of acute renal failure in *L. obliqua* envenomation is poorly understood. The difficulty of conducting early renal biopsies due the coagulation disturbances inherent to the incidents has contributed to this lack of knowledge. Although, the massive deposition of fibrin in the glomeruli capillaries due to intravascular coagulation and/or a direct action of the venom on the renal microcirculation cannot be discharged as causes of renal damage (Gamborgi et al., 2006).

Intracerebral hemorrhage is the main cause of deaths by *L. obliqua* envenomation. In the state of Paraná, also in Southern Brazil, hemorrhage of the central nervous system accounted for the death of 50% of *Lonomia*-envenomed patients registered from 1989 to 2005 (Kowacs et al., 2006). However, the mechanisms that lead to intracerebral hemorrhage in envenomed patients are also poorly understood.

3. Pharmacology and molecular aspects of experimental envenomation

The dramatic effects of *L. obliqua* venom in humans have been partially reproduced in a number of experimental