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A Pharmacological investigation of the scorpion venom effect on the cardio-hepatic tissues: Correlation with inflammatory response

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Severe scorpion envenoming is characterized by multi-system-organ failure which may lead to instability of several physiological systems and death. These manifestations are due to the ability of the neurotoxin components activate sodium channels in nerve terminals with the subsequent release of neurotransmitters, specially acetylcholine and adrenaline. However, there is evidence to suggest that inflammatory mediators are also released. The objective of this study is to investigate the potential role of adrenergic and arachidonic acid pathways in cardiohepatic injury and in systemic inflammatory response after scorpion envenoming. Analysis of tissue damage and inflammatory response was carried out into mice (20 ± 2 g, n = 5) envenomed with *Androctonus australis hector* (Aah) scorpion venom (0.5 mg/kg, s.c. route) and pretreated by β1-adrenoceptor antagonist (Metoprolol, 5 mg/kg, i.p.) or cyclo-oxygenase (COX-1 and COX-2) inhibitor (Indomethacin, 5 mg/kg, i.p.) 30 minutes prior to the envenomation. Biochemical indicators of oxidative stress, metabolical and inflammatory markers were measured in sera and tissue homogenates (heart and liver) of envenomed mice. All results were expressed as the mean ± SD (n=5). The statistical significance of differences between groups was analyzed by a Student *t*-test

Obtained results showed that the inoculation of Aah venom induced severe disturbances in the cardio-hepatic tissues (edema, hemorrhagic, necrosis) 24 hours after envenomation. The inflammatory process induced by this venom is characterized by hyperleukocytosis (predominatly neutrophilia) associated with elevated high level of both nitrate/nitrite, metabolites of nitric oxide (NO) (13.91 µM ± 3.56, $p<0.05$ compared with the control group, n=5). The migration of neutrophils in heart and liver was confirmed by the release of myeloperoxidase and by histological analysis. High serum levels of metabolical biomarkers, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and creatine phospho-kinase (CPK-MB) correlate to the tissue lesions (192.6 ± 22.8 IU/L, 74 ± 12.5 IU/L, 1537 ± 67.9 IU/L, $p<0.05$ compared with the control group, n=5). Our results showed also that Aah venom induced overproduction of lipid peroxidation products (0.128 ± 0.089 µM, $p<0.01$ compared with the control group, n=5) coupled with antioxidant depletion in sera and tissues. In liver and heart, leukocytosis, nitric oxide release and cellular peroxidase activities were inhibited by previous treatment with cyclo-oxygenase inhibitor. However, fluid accumulation in these organs and tissue damage seem to be partially reduced. Administration of Metoprolol β1-adrenergic blocker induces a significant decrease of edema and normalization of liver and heart enzymes (AST, ALT and CPK-MB). Histological analysis confirmed the inhibition of edema forming and the cell membrane integrity in cardio-hepatic tissues compared to envenomed mice. However, high lipid peroxidation rates and lower antioxidative protection were found in the liver and heart homogenates after inhibition β1-adrenoceptor or prostanoids mediators. In conclusion, cardio-hepatic damage induced by scorpion venom could be mediated partially by the activation of the sympathetic nervous system through the β1 adrenergic receptors and by lipid mediators. The use of antioxidants after scorpion envenomation could be also useful to produce a protective effect against deleterious manifestations and damages induced by the scorpion venom.