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Analgesic and side effects in rodents of Phα1β a spider venom toxin calcium channel blocker

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Calcium influx through neuronal voltage-sensitive calcium channels (VSCCs) mediates nociceptive information in the spinal dorsal horn. Phα1β is a peptide purified from the venom of the Brazilian armed spider Phoneutria nigriventer that reversibly and non-specifically inhibited high-voltage-activated Ca2+ channels, namely L-(Ca v 1.2), N-(Ca v 2.2), P/Q-(Ca v 2.1), and R-(Ca v 2.3) type, with varying potency (N > R > P/Q > L) in heterologous and native systems. We compared the antinociceptive and adverse effects induced by Phα1β and ω-conotoxin MVIIA, a specific N-type calcium channel blocker, in rodent models of pain. Spinally administered Phα1β showed higher efficacy and long-lasting analgesia than ω-conotoxin MVIIA. Phα1β had a therapeutic index wider (16) than ω- conotoxin MVIIA (4) also inducing less side effects than the conus toxin. Both toxins reversed an established pain but ω-conotoxin is less potent to produce such effect than Phα1β. VSCCs in the spinal cord have an importantrole modulating the release of key pro-nociceptive neurotransmitters, glutamate. Both toxins were able to reduce glutamate from cerebro spinal fluid but Phα1β presented potency about 3 times higher than ω-conotoxin MVIIA to block the evoked release of glutamate. We also investigated the analgesic effect of Phα1β in a model of cancer pain induced by inoculation of melanoma B16F10 into mice with or without tolerance to morphine analgesia. Phα1β was capable of controlling cancer-related pain even in mice tolerant to morphine antinociception inhibition and, more important, was also able to partially restore morphine analgesia in such animals. Phα1β is a ω-toxin with high therapeutic index and a broader action on calcium channels. It shows analgesic effect in several rodents' models of pain suggesting that this toxin has the potential to be used in clinical setting as a drug in the control of persistent pathological pain.

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Assesment of the antigenotoxic activity of hymenoptera venoms by assays with Hepg2 cells

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Hymenoptera venoms are constituted by a complex mixture of chemically or pharmacologically bioactive agents and that may also contain substances capable of inhibiting and/or decreasing the genotoxic action of other compounds that are able to induce damages in the genetic material. In this study we evaluated the cytotoxic, genotoxic and antigenotoxic activities of the venoms of the bee *Apis mellifera* and of the wasp *Polybia paulista* using the HepG2 test system. We used 3 concentrations that were considered non cytotoxic to evaluate the genotoxic potential of the venoms (comet assay and micronucleus test). It was observed that these concentrations were genotoxic, therefore we used lowest concentrations to assess the antigenotoxic effects. These new concentrations showed that both venoms, instead of inhibiting and/or diminishing the genotoxic effect of methyl methane sulfonate (substance used as positive control), increased even more the damages caused by this compound. It was also observed that both venoms were able to induce lipid per oxidation and alter the activities of some antioxidant enzymes (CAT, SOD, and GST). Thus, the genotoxicity of the venoms could be caused by the induction of reactive oxygen species (ROS) that interacted with biological membranes and with the DNA of the exposed cells. From this study, we can conclude that the use of Hymenoptera venoms for pharmacological purposes, for example in the treatments of cancer, should be done with extreme caution, since it was observed that even very low concentrations of these bioactive compounds can induce genotoxicity for human cells, as observed in the HepG2 cells.

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