Marcus Vinicius Gomez, J Bioequiv Availab 2011, 3:7
doi: http://dx.doi.org/10.4172/0975-0851.1000109

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference & Exhibition on
Pharmaceutical Regulatory Affairs
6-7 September 2011 Baltimore, USA

Brazilian toxins targeting channels involved in pain, ischemia and cardiac arrhythmias

Marcus Vinicius Gomez[1,2], A. H. Souza[1], C. Castro Junior[1,2], F.K. Rigo[3], I.A. Souza[1], M.A. M. Prado[4], V.F. Prado[4], J. Ferreira[3]

[1]Medical School, UFMG
[2]IEP Santa Casa BH
[3]Federal University Santa Maria RGS
[4]Robarts Research Institute, USA

One peptide toxin, purified from the venom of the spider *Phoneutria nigriventer* Tx3-6 shows more specificity for N-type calcium channels expressed in heterologous system HEK cells and was tested in different models of pain. Tx3-6 was as effective and potent as ω-conotoxin MVIIA to produce antinociception and was patented with the name of Phα1β. Comparing its antinociceptive action with morphine, Phα1β showed higher potency and longer lasting effect. When administered before formalin injection (pretreatment), Phα1β was as effective and potent as ω-conotoxin MVIIA to produce antinociception but Pha1b was more effective to reverse an established nociceptive process (postreatment) than conotoxin MVIIA. Pha1b had antinociceptive action in acute and chronic pain. In cancer pain of rodents, the treatment with Phα1β and MVIIA showed a long-lasting action. When side effects were assessed, Phα1β had a therapeutic index 4 times wider than ω-conotoxin MVIIA and this toxin were 2.2 times more toxic than Pha1b. In the spinal cord the neurotransmitter glutamate is an important mediator of pain. Formalin injection induces pain and increases glutamate levels in cerebrospinal fluid (CSF) of rats. Phα1β and ω-conotoxin almost blocked the increase in CSF glutamate levels induced by formalin. The recombinant Phα1β repeats the effects of the native toxin. Capsaicin-stimulated glutamate release from spinal cord synaptosomes was inhibited by both Phα1β and ω-conotoxin MVIIA but IC50 for the spider toxin was 2.2 times lower than that of ω-conotoxin MVIIA. Capsaicin is an agonist of TRPV1 receptor and we tested the action of the Phα1β on capsaicin-induced calcium transients of DRG neurons and HEK cells expressing TRPV1 receptor. The inhibitory actions of Phα1β and SB366791 (antagonist of TRPV1 receptor) on capsaicin-induced calcium transients in DRG neurons were not additive, suggesting they act on the same pathway.The specific binding of [^{3}H]-resiniferatoxin (3H-RTX) in DRG membranes decreased by capsaicin and neither SB366791, a TRPV1 antagonist nor Phα1β were able to alter [^{3}H]-RTX binding. Thus, the interaction of Phα1β with TRPV1 does not occur at the intracellular site of the TRPV1 receptor. The toxin prevents capsaicin-induced nociception using a TRPV1 pathway but without binding directly to this receptor.

The spider toxin Tx3-4 is a calcium channel blocker N-and P/Q types and has neuroprotective effect of hippocampus and retinal tissues submitted to ischemia induced by oxygen and glucose deprivation. The toxin inhibits the glutamate release induced by the ischemia process and induces neuroprotection even whem applied after the onset of the ischemia in hippocampus and retinal tissues.

Tx3-1 also named as PhKv blocks voltage activated A-type potassium currents in the GH3 neuroendocrinal cell line. PhKv reduced the duration of ventricular arrhythmias induced by occlusion of the left anterior descending coronary. This effect was blocked by atropine, thereby indicating the participation of muscarinic.