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Isolation and Characterization of the First Known Inhibitor Cystine Knot Peptide in Sea Anemone: Inhibitory Activity on Acid-Sensing Ion Channels

Authors : Armando A. Rodríguez, Emilio Salceda, Anoland Garateix, André J. Zaharenko, Steve Peigneur, Omar López, Tirso Pons, Michael Richardson, Maylín Díaz, Yasnay Hernández, Ludger Ständker, Jan Tytgat, Enrique Soto

Abstract : Acid-sensing ion channels are cation (Na+) channels activated by a pH drop. These proteins belong to the ENaC/degenerin superfamily of sodium channels. ASICs are involved in sensory perception, synaptic plasticity, learning, memory formation, cell migration and proliferation, nociception, and neurodegenerative disorders, among other processes; therefore those molecules that specifically target these channels are of growing pharmacological and biomedical interest. Sea anemones produce a large variety of ion channels peptide toxins; however, those acting on ligand-gated ion channels, such as Glu-gated, Ach-gated ion channels, and acid-sensing ion channels (ASICs), remain barely explored. The peptide PhcrTx1 is the first compound characterized from the sea anemone Phymanthus crucifer, and it constitutes a novel ASIC inhibitor. This peptide was purified by chromatographic techniques and pharmacologically characterized on acid-sensing ion channels of mammalian neurons using patch-clamp techniques. PhcrTx1 inhibited ASIC currents with an IC50 of 100 nM. Edman degradation yielded a sequence of 32 amino acids residues, with a molecular mass of 3477 Da by MALDI-TOF. No similarity to known sea anemone peptides was found in protein databases. The computational analysis of Cys-pattern and secondary structure arrangement suggested that this is a structurally ICK (Inhibitor Cystine Knot)-type peptide, a scaffold that had not been found in sea anemones but in other venomous organisms. These results show that PhcrTx1 represents the first member of a new structural group of sea anemones toxins acting on ASICs. Also, this peptide constitutes a novel template for the development of drugs against pathologies related to ASICs function.

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