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Sea Anemone Kunitz Peptide Hciq2c1: Nmr Structure, Modulation of Trpa1 Channel, Anti-inflammatory Activity and Suppression of Nociceptive Reaction In Vivo

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TRPA1 is a homotetrameric non-selective calcium-permeable channel responsible for acute pain sensation and inflammation. Here, we showed that HCIQ2c1 peptide from the sea anemone Heteractis magnifica significantly reduces AITC-, capsaicin- and carrageenan-induced pain, inflammation and edema in mice. The peptide attenuates the systemic and local inflammatory effects through the inhibition of intracellular Ca2+ release, the production of ROS and pro-inflammatory cytokines, and enzymes involved in arachidonic acid metabolism. Electrophysiology recordings revealed that HCIQ2c1 binds to open TRPA1 channel and prevents its transition to closed or inhibitor-insensitive 'hyperactivated' states. 1H-15N NMR study described a classical Kunitz-type structure and revealed two dynamic hot-spots mobile on ps–ns and μs–ms timescales. The binding of HCIQ2c1 to the isolated voltage-sensing-like domain (VSLD) of the TRPA1 channel was observed by NMR in the LPPG micelles. In modelled HCIQ2c1/TRPA1 complex, the peptide interacts simultaneously with VSLD and pore domain, thus explaining stabilization of the specific channel state(s), which is probably responsible for the observed analgetic activity. HCIQ2c1 is the third peptide ligand of TRPA1 from sea anemones and the first Kunitz-type ligand of this channel.

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