Spider-venom peptides that target the human $Na_v1.7$ channel: potential analgesics for the treatment of chronic pain

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The voltage-gated sodium channel 1.7 ($Na_V1.7$) has recently emerged as a promising analgesic target. Gain-of-function mutations in the *SNC9A* gene encoding the pore-forming α-subunit of $Na_V1.7$ cause painful inherited neuropathies whereas loss-of-function mutations result in a congenital indifference to all forms of pain. Thus, selective blockers of $Na_V1.7$ are likely to be powerful analgesics. However, $Na_V1.7$ is only one of nine human Na_V subtypes, and improper function of certain members of this ion channel family can cause debilitating or even lethal channelopathies. Thus, therapeutics designed to target $Na_V1.7$ must have exquisite selectivity. Of particular concern for a $Na_V1.7$-targeted analgesic would be off-target effects on $Na_V1.5$, which is responsible for the rising phase of the cardiac action potential, or the muscle-specific subtype $Na_V1.4$.

Modulation of Na_V channels is a dominant pharmacology in spider venoms, and hence we decided to screen an extensive panel of >200 spider venoms for blockers of this channel. Using an in-house, high-throughput FLIPR-based screen, 36% of all spider venoms that we assayed were found to contain potent blockers of the human $Na_V1.7$ channel. Using this assay, we purified a total of 41 peptidic blockers of human $Na_V1.7$ from 25 “hit” venoms. Sequencing of these peptides revealed that they fall into three distinct structural classes, although they all contain three disulfide bonds.

One of these structural classes, which contains a large number of related toxins that nevertheless have diverse selectivities against the various Na_V subtypes is of particular interest. Toxins from this family inhibit Na_V channel activation by binding to the voltage sensor of channel domain II. A novel approach for rapidly mapping the pharmacophore of these toxins circumvents the need to produce and purify mutant toxins. Careful structural and functional characterization of this family of toxins is providing detailed information on the residues responsible for the interaction of these toxins not just with the desired therapeutic target ($Na_V1.7$) but also critical off-target subtypes such as $Na_V1.5$. It is anticipated that development of detailed structure-function relationships for this class of toxins will enable us to engineer highly specific blockers of the human $Na_V1.7$ channel that will be therapeutically useful for the treatment of chronic pain.

Structural, functional, and *in vivo* analgesic data will be presented for one novel peptide with more than 100-fold selectivity for $Na_V1.7$ over the critical off-target subtypes $Na_V1.4$ and $Na_V1.5$.