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Multi-scale evaluation of spider toxins as potential anti-nociceptive agents: Example of Cyriotoxin-1a

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Nav_v1.7 channel subtype is highly expressed in dorsal root ganglia (DRG) and plays a key role in pain signaling. We performed high-throughput screening of an original animal venom library, using automated patch-clamp experiments on human Nav_v channel subtypes, to find new selective inhibitors of this target (1), and then in vitro and in vivo electrophysiological experiments to characterize the active peptides that have been purified, sequenced and chemically synthesized (2). We identified a novel peptide, Cyriotoxin-1a (CyrTx-1a), isolated from Cyriopagopus schioedtei spider venom (1). This 33 amino acids toxin inhibits hNav_v1.1-1.3 and 1.6-1.7 in the low nanomolar range, compared to the micromolar range for hNav_v1.4-1.5 and 1.8. CyrTx-1a is 920 times more efficient at inhibiting tetrodotoxin (TTX)-sensitive than TTX-resistant Na currents of adult mouse DRG neurons in vitro, and approximately 170 times less efficient than huwentoxin-IV at altering mouse skeletal neuromuscular excitability in vivo. Finally, CyrTx-1a exhibits analgesic effects in mice by significantly increasing reaction time in the hot-plate assay (2). These results pave the way for further engineering studies aimed to optimize the potential anti-nociceptive properties of CyrTx-1a.

