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***In vivo* evaluation of antinociceptive effects of cyriotoxin-1a, the first toxin purified from *Cyriopagopus schioedtei* spider venom**

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Over the past two decades, animal venom toxins have been widely explored as an original source of new antinociceptive drugs directed towards the Nav1.7 subtype of voltage-gated sodium channels. This subtype, expressed in afferent sensitive fibers and more particularly in dorsal root ganglia (DRG) neurons, has been validated as an antinociceptive target of choice by human genetic evidence such as congenital insensitivity to pain [1].

High throughput screening of Smartox biotechnology company collection venoms, using automated patch-clamp (QPatch HTX, Sophion Biosciences) on HEK cells overexpressing human Nav subtypes, pointed out a new inhibitory cysteine knot (ICK) toxin, named cyriotoxin-1a (CyrTx-1a). In DRG neurons isolated from adult mice, the peptide preferentially inhibited with high affinity tetrodotoxin (TTX)-sensitive Na current ($IC_{50} = 170$ nM), flowing through mainly the Nav1.7 subtype, compared to TTX-resistant Na current ($IC_{50} = 108$ μ M), flowing through Nav1.8 and Nav1.9 subtypes. In addition, the peptide exhibited nanomolar range affinity for Nav1.7, Nav1.1-1.3 and Nav1.6 subtypes and micromolar range affinity for Nav1.5 and Nav1.4 subtypes. The hot plate and von Frey pain assays showed that mice injected with 367 μ g/kg of CyrTx-1a were more resistant to pain than animals injected with the vehicle (PBS). However, compound muscle action potential (CMAP) recordings after toxin injection revealed a relative narrow therapeutic window w/o side-effects.

In conclusion, the pharmacological profile of CyrTx-1a is of great interest since it leads to further engineering studies aimed to improve its selectivity for optimizing the use of this peptide as an antinociceptive therapeutics.

Ribbon representation of the backbone peptide folding of CyrTx-1a determined by ¹H 2D NMR method. The structural topology of the double-stranded antiparallel β -sheet (arrows) was identified by Pymol. The three disulfide bonds are C2–C17, C9–C22 and C16–C29 (in yellow). Hydrophobic residues are colored in green, and basic and acidic residues are colored in blue and red, respectively. The other polar residues are colored in white.

References:

[1].Vetter et al. (2016) Nav1.7 as a pain target – from gene to pharmacology. *Pharmacology and Therapeutics* 172, 73-100.

