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## Antinociceptive evaluation of cyriotoxin-1a and huwentoxin-IV, two spider toxins that block with high affinity the Nav1.7 subtype of voltage-gated sodium channels

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Over the last decades, animal venom toxins have been explored as an original source of new antinociceptive drugs. Our target of interest, Nav1.7, has been validated by human genetic evidence and is mainly expressed in dorsal root ganglia (DRG) neurons. High throughput screening of Sanofi's collection of venom toxins was performed on HEK cells overexpressing human Nav subtypes. The results highlight a new toxin, cyriotoxin-1a (CyrTx-1a), sharing the same inhibitory cysteine knot (ICK) motif with toxins originating from the same theraphosids spider family, such as huwentoxin-IV (HwTx-IV), a potential analgesic targeting Nav1.7. However, when tested in mouse isolated neuromuscular preparations at low concentrations (that did not affect the Nav1.4 muscle subtype), HwTx-IV inhibited completely the muscle contraction, thus incriminating the Nav1.6 neuronal subtype. CyrTx-1a and HwTx-IV revealed nanomolar range affinity for Nav1.7, 1.6, 1.1, 1.2 and 1.3 and micromolar range affinity for Nav1.5, 1.4 and 1.8. Moreover, in mouse DRG neurons, the peptides inhibited preferentially tetrodotoxin (TTX)-sensitive Na current flowing mainly through Nav1.7, compared with TTX-resistant Na current flowing through Nav1.8 and 1.9. Within a therapeutic window of concentrations sparing skeletal muscular system, the peptides exhibited a similar analgesic-like effect in mouse pain models (hot plate and von Frey essays). However, compared with HwTx-IV, CyrTx-1a had less marked *in vivo* side-effects, as detected by analyzing *in vivo* the excitability properties of the mouse neuromuscular system, mediated by Nav1.4 and 1.6. In conclusion, the better *in vivo* pharmacological profile of CyrTx-1a paves the way for further engineering studies aimed to optimize its potential antinociceptive capability.