New twists in old tales. Conotoxins targetted to sodium channels

R.S. Norton, The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, VIC 3050, Australia.

The fish-hunting cone snail *Conus radiatus* produces a novel conotoxin, ι-RXIA, which is a member of the recently characterized I_1-superfamily. This superfamily contains eight cysteine residues arranged in a –C-C-CC-CC-C-C- pattern. ι-RXIA is one of several I_1 peptides in which the third last residue is post-translationally isomerized to the D-configuration, and naturally occurring ι-RXIA, with D-Phe44, is significantly more active as an excitotoxin than the L-Pheanalogue both *in vitro* and *in vivo*. We have determined the solution structures of both forms by NMR spectroscopy (Buczek *et al.*, 2007). The structure of ι-RXIA is well defined up to around residue 35 and adopts an ICK structure. The C-terminal region, including Phe44, is disordered. Comparison of the D-Phe44 and L-Phe44 forms indicates that the switch from one enantiomer to the other has very little effect on the structure, even though it is clearly important for receptor interaction based on activity data. Finally, we identify the target of ι-RXIA as a voltage-gated sodium channel. ι-RXIA is an agonist, shifting the voltage dependence of activation of mouse $Na_V1.6$ expressed in *Xenopus* oocytes to more hyperpolarized potentials. Thus, there is a convergence of structure and function in ι-RXIA, as its disulfide pairing and structure resemble those of funnel web spider toxins that also target sodium channels.

Voltage-gated sodium channels are a target for several families of conotoxin. Recently, new representatives of the μ-conotoxin family have been described and their structures determined (Keizer *et al.*, 2003; Bulaj *et al.*, 2005). These suggest a potential of these toxins in the treatment of pain (Green *et al.*, 2007).

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