Decorated venom: Sulfation and amidation of alpha-conotoxins

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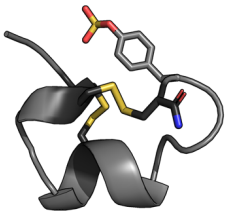
Conotoxins are peptides found in the venoms of marine cone snails. Many conotoxins are highly structured and stable and have potent activities at neuronal and muscle receptors, which make them valuable probes to understand these receptors and promising lead molecules for drug development. Many conotoxins are also highly modified with posttranslational modifications, the roles of which are poorly understood at a structural and functional level; it is unclear whether the modifications interact directly with the binding site, alter conotoxin structure, or both. In this presentation, I will discuss our work on the known conotoxins bearing posttranslational modifications in the form of native sulfotyrosine and C-terminal amidation and show that these two modifications in combination increase their activity at nicotinic acetylcholine receptors and binding to soluble acetylcholine binding proteins, respectively. We rationalise how these functional differences between variants might arise from stabilization of the three-dimensional structures and interactions with the binding sites, using high-resolution Nuclear Magnetic Resonance data. This work illustrates that posttranslational modifications can modulate interactions between a ligand and receptor by a combination of structural and binding alterations. A deeper mechanistic understanding of the role of posttranslational modifications in structure-activity relationships is essential for understanding receptor biology and could help to guide structure-based drug design.



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