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# Structural Comparison of Three Crystalline Complexes of a Peptidic Toxin With a Synaptic Acetylcholine Recognition Protein

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Many peptidic toxins from animal venoms target neuronal or peripheral synaptic receptors with high affinities and specificities. Hence, these toxins are not only potent natural weapons but also precise molecular tools for pharmacological studies of their receptors. Although they belong to various structural and/or functional subfamilies, they often share similar molecular features, such as a highly reticulated scaffold presenting specific binding determinants.

The three-fingered toxin from mamba venom, fasciculin (Fas2), is a noncompetitive inhibitor of acetylcholinesterase (AChE). The crystal structure of Fas2 bound to the peripheral anionic site of the mouse enzyme provided the first view of a natural peptidic toxin bound to a synaptic ACh-recognition protein (Bourne et al., 1995). The three-fingered, long α-neurotoxin from cobra venom, α-cobratoxin, is a competitive antagonist for the nicotinic ACh receptor (nAChR). The structure of α-cobratoxin bound to the pentameric ACh-binding protein (AChBP) from *Lymnaea stagnalis*, a soluble surrogate of the neuronal receptor subtype α7, revealed the position and orientation of the toxin molecule inserted at the AChBP subunit interface and the conformational changes associated with toxin binding (Bourne et al., 2005). The small neuropeptide from marine cone, α-conotoxin ImI, is also a competitive antagonist for the nAChR. The recent structure of ImI bound to the AChBP from *Aplysia californica* (Hansen et al., 2005) shows a near-buried ImI that entirely fills the ligand-binding pocket at the subunit interface and promotes conformational changes in the receptor that differ from those observed with α-cobratoxin. Comparison of this structure to that, independently solved, of a PnIA double variant bound to the same AChBP (Celie et al., 2005) reveals molecular adaptability in the modes of binding for the two conopeptides. All

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three complexes are stabilized by both aromatic and cation-aromatic interactions between the bound toxin and its receptor, consistent with their subnanomolar dissociation constants.

These structures, which provide alternative templates for better understanding of the selectivity of the various peptidic toxins for the various ACh-recognition proteins, will be presented comparatively and their common/distinctive features will be discussed.

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