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Diversity in the binding interactions of nicotinic ligands and toxins to the nAChRs and associated conformational fluctuations - Insights into the core motif dictating antagonism

Yves BOURNE¹, Gerlind SULZENBACHER¹, Zoran RADIĆ², Laurent CHABAUD³, Rómulo ARÁOZ⁴, Evelyne BENOIT⁴, Armen ZAKARIAN⁵, Denis SERVENT⁴, Catherine GUILLOU³, Palmer TAYLOR², Jordi MOLGÓ⁴, Pascale MARCHOT^{1,*}

¹*Architecture et Fonction des Macromolécules Biologiques, CNRS/AMU, Faculté des Sciences - Campus Luminy, Marseille.* ²*Skaggs School of Pharmacy and Pharmaceutical Sciences, Dept. Pharmacology, UC San Diego, La Jolla, CA, USA.* ³*Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France.* ⁴*Institut des sciences du vivant Frédéric Joliot, CEA Paris-Saclay, Gif-sur-Yvette, France.* ⁵*Dept. Chemistry and Biochemistry, UCSB, Santa Barbara, CA, USA.*

*Corresponding author, e-mail: pascale.marchot@univ-amu.fr

The pentameric ACh-binding proteins (AChBP) from water snails are soluble structural and pharmacological surrogates of the extracellular, ligand-binding domain of nicotinic ACh receptors (nAChRs)¹. As such they offer pertinent models for studying the modes of binding of nicotinic effectors and the associated conformational changes, and correlate them with functional alteration of the nAChR channel. Crystal structures of AChBP complexes revealed that nicotinic agonists and competitive antagonists bind primarily within a nest of aromatic side chains, contributed by loops C and F located on opposing faces of each subunit interface, and induce a range of loop C conformations that modulate the size and shape of the binding pocket²⁻⁴.

The macrocyclic imine phycotoxins belong to an emerging class of chemical agents associated with marine algal blooms and shellfish toxicity. Binding and voltage-clamp recordings on muscle-type and neuronal nAChRs revealed subnanomolar affinities dictated by slow dissociation, potent antagonism, and varying levels of nAChR subtype selectivity. Crystal structures of the complexes showed that common AChBP determinants imbedded within the aromatic nest confer high affinity binding to the toxins, while distinctive determinants brought about by loop F and located within the nest, or extending outside the nest towards apical, radial or 'membrane' subsites of the interface, dictate either broad or narrow nAChR subtype selectivity by the toxins⁵⁻⁷.

Based on these data, new organic compounds aimed at pinpointing the minimal chemical motif that dictates antagonism were designed, synthesized and analyzed relative to nAChRs and AChBP⁸. Structural analysis of the complexes showed that the spiroimine core common to these compounds is the major component of their mode of binding, while the surrounding substituents are involved into nAChR subtype specificity.

These data identify distinctive ligands, functional determinants and binding sites for the design of new drugs targeting disease-associated nAChR subtypes.

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¹Smit et al (2003) *Ann NY Acad Sci* 998:81-92. Review.

²Bourne et al (2005) *EMBO J* 24:1512-22.

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⁴Hibbs, Sulzenbacher, et al (2009) *EMBO J* 28:3040-51.

⁵Bourne et al (2010) *Proc Natl Acad Sci USA* 107:6076-81.

⁶Bourne et al (2015) *Structure* 23:1106-15.

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⁸Marchot & coll, manuscript in preparation.

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