Backbone cyclization turns a venom peptide into a stable and equipotent ligand at both muscle and neuronal nicotinic receptors

Julien Giribaldi[1], Yves Haufe[2], Edward Evans[3], Muriel Amar[4], Anna Durner[2], Casey Schmidt[3], Adèle Faucherre[5], Hamid Moha Ou Maati[5], Christine Enjalbal[1], Jordi Molgó[4,6], Denis Servent[4], David T. Wilson[3], Norelle L. Daly[3], Annette Nicke[2] and Sébastien Dutertre

[1]Institut des Biomolécules Max Mousseron, UMR 5247, Université de Montpellier, CNRS, 34095 Montpellier, France.

[2]Walther Straub Institute of Pharmacology and Toxicology, Faculty of Medicine, LMU Munich, Nußbaumstraße 26, 80336 Munich, Germany.

[3]Centre for Molecular Therapeutics, Australian Institute of Tropical Health and Medicine, James Cook University, Cairns, QLD 4878, Australia.

[4]Commissariat à l'Energie Atomique et aux énergies Alternatives (CEA), Institut des Sciences du Vivant Frédéric Joliot, Service d'Ingénierie Moléculaire des Protéines (SIMOPRO), CEA de Saclay, Université Paris-Saclay, F-91191 Gif-sur-Yvette, France.

[5]Département de Physiologie, Institut de Génomique Fonctionnelle, CNRS/INSERM UMR 5203, Université de Montpellier, 34095 Montpellier, France.

[6]Institut des Neurosciences Paris-Saclay, UMR 9197 CNRS/Université Paris-Sud, 91198 Gif-sur-Yvette, France.

sebastien.dutertre@umontpellier.fr

Venom peptides are promising drug leads but their therapeutic use is often limited by stability and bioavailability issues. In this study, we designed cyclic analogues of α-conotoxin CIA, a potent muscle nicotinic acetylcholine receptor (nAChR) blocker with significantly lower affinity at the neuronal α3β2 subtype. Remarkably, all analogues retained the low nanomolar activity of native CIA towards muscle-type nAChRs but showed greatly improved resistance to degradation in human serum and, surprisingly, displayed up to 52-fold higher potency for the α3β2 neuronal nAChR subtype (IC50 1.3 nM). Comparison of NMR-derived structures revealed some differences that might explain the gain of potency at α3β2 nAChRs. All peptides were highly paralytic when injected into adult zebrafish and bath-applied to zebrafish larvae, suggesting barrier-crossing capabilities. Finally, these cyclic CIA analogues were shown to be unique pharmacological tools to investigate the contribution of the presynaptic α3β2 nAChR subtype to the train of four (TOF) fade.