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From peptide and protein neurotoxins to receptor structure-function and new drugs

Alpha-Neurotoxins, snake venoms proteins, earlier helped to isolate nicotinic acetylcholine receptors (nAChRs) and are still precious tools in their research. The nAChRs are involved in muscle contraction, cognition, immune system activity. nAChR malfunctioning is associated with muscle dystrophies, psychiatric and neurodegenerative diseases, cancer. Another tool in nAChR research is α -conotoxins, neurotoxic peptides from *Conus* snails. Analysis of nAChR interactions with α -neurotoxins and α -conotoxins provided information about binding surfaces required for drug design. The lecture will cover research at our department in collaboration with European laboratories. First X-ray structure for α -conotoxin complexes with their biological targets was for α -conotoxin PnIA [A10, K14] bound to acetylcholine-binding protein (AChBP); recently from this α -conotoxin several more potent and selective analogs were prepared. Dimeric α -cobratoxin was discovered wherein two α -cobratoxins are joined by 2 intermolecular S-S-bonds; this post-translational modification retained blocking of $\alpha 7$ and muscle-type nAChRs but added inhibition of $\alpha 3\beta 2$ nAChRs; X-ray analysis revealed unusual packing. α -Bungarotoxin and α -cobratoxin, two closely related α -neurotoxins, block $\alpha 7$ and muscle-type nAChRs with similar affinity; recently we demonstrated that they also block GABA-A receptors, some receptor subtypes being more sensitive to α -cobratoxin. Structurally, α -neurotoxins resemble some mammalian proteins of Ly6 family which modulate the nAChR activity; water-soluble analog of Lynx1 bound competitively to AChBP and muscle-type nAChRs, but non-competitively to neuronal ones.

Biography

Victor Tsetlin has received his PhD in 1973, from 1996 he is a Professor and from 2006 he is the corresponding Member of the Russian Academy of Sciences, Head of the Department. He was a Visiting Scientist at Imperial College, London in 1985 and Visiting Professor at Free University of Berlin in 1993-1995. He was a Member of ESN Council in 1999-2009, Member of the Advisory Board of the *EJB-FEBS Journal* in 2000-2011 and from 2013 Member of the Advisory Board at the *Biochemical Journal*. He is the author of over 250 publications in many journals among them *Journal of Neurochemistry*, *Journal of Biological Chemistry*, *Proceedings of National Academy of Sciences, USA*, *Nature Structural and Molecular Biology*, *Trends in Pharmacological Science*.

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