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FROM THE INTERACTION OF NEUROTOXIC PEPTIDES AND PROTEINS WITH THE CYS-LOOP RECEPTORS TO NOVEL DRUGS

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The talk is devoted to research on neurotoxic proteins and peptides carried out at our Institute in collaboration with leading Russian and foreign laboratories. It focuses on toxins interacting with nicotinic acetylcholine receptors (nAChRs) and other Cys-loop receptors : glycine receptors (GlyR), ionotropiic γ-aminobutyric acid and serotonin GABA-A and 5HT-3 receptors. Due to high homology, identification of functionally active individual subtypes cannot be reliably performed with antibodies and neurotoxins are more preferable because many have a considerable selectivity to a particular receptor subtype which can even be increased by design of novel analogs and derivatives. X-ray analysis of the neurotoxin complexes with Cys-loop receptors or receptor models, such as the acetylcholine-binding proteins (AChBPs) or receptor ligand-binding domains (LBD), provided information about the receptor binding sites opening new ways to drug design. These lines are illustrated by our recent work: using a novel computer program, α-conotoxin PnIA analogs were designed, synthesized, tested by radioligand analysis, electrophysiology and Ca2+ imaging and shown to have extremely high affinity for neuronal α7 nAChR which plays an important role in the neuroimmune axis and is a well-known target in drug design. Another example is a linear peptide azemiopsin isolated from the viper venom: contrary to all earlier known peptides and proteins from animal venoms which inhibit nAChRs and contain from 1 to 5 disulfides, azemiopsin has no disulfide bridges (thus greatly simplifying its synthesis) but selectively blocks the muscle nAChRs; its preclinical studies as a promising myorelaxant have been recently published. New ways to drug design can emerge from the discovered interactions of the human endogenous proteins with the Cys-loop receptors: it was recently shown that human SLURP-1 (protein of the Ly6 family having the same three-finger folding as snake venom α-neurotoxins) allosterically inhibits α9 nAChR, a target for novel analgesics.

Biography

V.Tsetlin has got Ph.D. and D. Sci. degrees in chemistry (1973, 1987) at the Shemyakin-Ovchinnikov Institute; now Head of the Department of Molecular Basis of Neurosignaling. Professor (1996) and corresponding member of the Russian Academy of Sciences (2006). The awards: Russian State Prize in Science and Technology (1985), the Humboldt Prize (1992); invited scientist at the Uppsala University, Imperial College (London), Institute of Protein Research (Osaka), Free University (Berlin). Member of the Advisory Board of FEBS J. (2000-2011), Biochem. J. (2013-present). Published over 200 papers: in PNAS, Neuron, Nature Str. Mol. Biol, J.Biol.Chem., J. Neurochemistry, TIPS, Sci. Rep., Neuropharmacology.

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