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Similar effects of peptides and proteins from animal venoms and of human Ly-6 proteins on nicotinic receptors

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In the frames of the organized conference the term "biosimilar" is apparently most applicable to compounds which in principle should be identical but, especially if produced by heterologous expression in different laboratories, may differ in the degree of purification or other properties which are difficult to control. On the other hand, of great interest is "biosimilarity" as a manifestation of similar biological activity produced by compounds of absolutely different structure. In the proposed lecture it will be illustrated by interaction of various naturally-occurring and designed/ synthesized compounds with various subtypes of nicotinic acetylcholine receptors (nAChRs). The similarity in the effects of various compounds appears when they attach roughly at the same binding site at the nAChRs. α-Neurotoxins from snake venoms have played a crucial role in earlier isolation of muscle-type nAChRs and at present are a good pharmacological tool for identifying muscle-type and neuronal α7 nAChRs. Their binding site is situated in the receptor ligand-binding domain (LBD) at the interfaces between the subunits, as earlier shown by "wet" biochemistry and then confirmed by the X-ray analysis. Another class of sophisticated tools for research on nAChRs are α-conotoxins, neurotoxic peptides from *Conus* marine snails which not only allow to distinguish muscle nAChRs from the neuronal ones, but also help to identify individual subtypes of neuronal receptors. α-Conotoxins as such or as modified forms are considered as promising drugs, in particular those selective for the α9 nAChR may give new analgesics. The deviations from "biosimilarity" might arise if some of the structurally similar compounds have additional targets: for example, we found that α-cobratoxin, a classical blocker of muscle and neuronal α7 nAChR can also inhibit certain subtypes of GABA-A receptor and weak inhibitory activity against this receptor was manifested by several α-conotoxins. Some activities, when measured by one method may be similar, but differ when tested by another method. For example, α-cobratoxin, such α-conotoxins as PnIA analogs and Ly-6 proteins ws-Lynx1 and SLURP-1 (these proteins have the same three-finger folding as α-cobratoxin) inhibit ion currents in the α7 nAChR (with the affinity decreasing in this series) according to electrophysiology experiments, while radioligand analysis revealed that α-cobratoxin and α-conotoxins bind to the orthosteric site in the receptor, but the Ly-6 proteins attach in the allosteric one.

Recent Publications

- Dutertre S, Nicke A and Tsetlin V I (2017) Nicotinic acetylcholine receptor inhibitors derived from snake and snail venoms. Neuropharmacology. 127:196-223.
- Kudryavtsev D S, Shelukhina I V, Son L V, Ojomoko L O, Kryukova E V et al. (2015) Neurotoxins from snake venoms and α-conotoxin ImI inhibit functionally active ionotropic γ-aminobutyric acid (GABA) receptors. J Biol. Chem. 290(37):22747-22758.
- Kasheverov I E, Chugunov A O, Kudryavtsev D S, Ivanov I A, Zhmak M N et al. (2016) High-affinity α-Conotoxin PnIA analogs designed on the basis of the protein surface topography method. Sci. Rep. 6:36848.
- Tsetlin V I (2015) Three-finger snake neurotoxins and Ly6 proteins targeting nicotinic acetylcholine receptors: pharmacological tools and endogenous modulators. Trends Pharmacol. Sci. 36(2):109-123.

Biography

Victor Tsetlin has got PhD and DSci 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). He received the following awards: Russian State Prize in Science and Technology (1985), and the Humboldt Prize (1992). He is an Invited Scientist at the Uppsala University, Imperial College (London), Institute of Protein Research (Osaka), Free University (Berlin). He is a Member of the Advisory Board of FEBS J (2000-2011), Biochem. J. (2013-present). He has published over 200 papers: in *PNAS, Neuron, Nature Str. Mol. Biol., J. Biol. Chem., J. Neurochemistry, TIPS, Sci. Rep., Neuropharmacology*.

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