HYDROPHOBIC ANISOTROPY OF SCORPION A-TOXINS SURFACE

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Voltage sensitive Na^+-channels (Na_vs) are integral membrane proteins that selectively control flow of Na^+ ions and participate in the generation and propagation of action potentials in excitable cells. Thus, Na_vs serve as one of the primary targets for various animal neurotoxins, such as scorpion toxins, binding of which alters the membrane potential and the channel activity. Alpha-toxins bind with high affinity to extracellular S3-S4 loop of domain IV of Na_vs pore-forming α-subunit (site 3), slowing channel inactivation and causing a prolonged action potential. According to their different pharmacological preferences, the scorpion α-toxins can be divided into three subgroups: classical (bind to one or more of nine mamal Na_vs subtypes), insect α-toxins (active on insect channels) and α-like (toxic to both mammal and insects).

Scorpion toxins have already proven to be important pharmacological tools for probing structure and binding surfaces of the Na_vs and studying the activation and inactivation processes. The search of structural and dynamic features of α-toxins that define selectivity to channels' subtypes is not only fundamentally significant, but also leads to further development of novel insecticides, based on insect-selective scorpion toxins.

α-Toxins (55-65 residues long) are composed of two evolutionary independent and functionally different "domains": Core-domain, formed by conservative throughout all toxins βαββ-fold, and so called RC-domain, which comprises N-terminal reverse turn (8-12 residues) and C-tail of a protein, that are pulled together by disulphide bond. Using molecular dynamics stimulations and molecular hydrophobicity approach we studied hydrophobic features of scorpion α-toxins surface and their conformational mobility. For the group of classic toxins we discovered that molecules have anisotropic hydrophobic features: RC-domain appears to be significantly more hydrophobic and flexible, comparing to Core-domain. For two insect-active groups there is no such difference between domains. Core-domain, which has similar hydrophobicity for all three toxin groups, is believed to bind to conservative channel surfaces that are invariant in either Na_v subtype, whereas RC-domain is thought to interact with variable between subtypes loops. These peculiarities should reflect some features of their channels' binding surfaces and may serve as a starting point for further discovery of species selectivity mechanism, as well as design of engineered analogs of insect-selective toxins.