MOLECULAR MODELING OF POTASSIUM CHANNELS COMPLEXES WITH SEVERAL SCORPION VENOM TOXINS

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Complicacy in the study of functional role of potassium channels and revealing an expression and activity levels of these channels in cells and tissue is related to restricted selectivity of known modulators or even to absence of highly selective ligands. That is why development of highly active and selective channel ligands is of exceptional importance. Our goal is the study of molecular basis for selectivity of interactions between peptide ligands and potassium channels, the development of principles and means for design of selective high-affinity potassium channel peptide blockers using molecular modeling.

For investigation of interaction between eukaryotic potassium channels and peptide ligands we used modified chimera prokaryotic KcsA channel in which the voltage-sensor paddle has been replaced by the voltage-sensor paddle from the eukaryotic channels, such as Kv1.1, Kv1.2, Kv1.3, Kv1.6. The channel-blocker complexes structural models were prepared by homology modelling. As a template we used the crystal structure of Kv1.2-2.1 paddle chimera channel in complex with charybdotoxin (CTX) (pdb-code 4JTA). CTX, a 37-residue peptide isolated from the venom of the scorpion, has a structure similar to agitoxin, hongotoxin, margatoxin, kaliotoxin and OSK that have used in our project. Toxin coordinates have been taken from the Protein Data Bank. The resulting structure was refined using MD simulations in the force field oplsaa. Special attention was paid to potassium ions in the pore of the channels. The pore of potassium channel contains four ion-binding sites that form a selectivity filter. When toxins bind to the channel, a lysine residue poised at a critical position on the toxin is so close to the outermost ion-binding site that it prevents potassium ions binding to the site. To find optimal orientation of the toxins we rotated toxins in binding site at 5° intervals along the channel axis while maintaining the position of important Lys27(28) relative to the selective filter. Since the channel has fourfold symmetry, the rotation only spans 90°. We performed the cluster analysis and chose clusters with high level of electrostatic interactions as a preferable. Obtained results were compared with a direct method of binding energy calculation – potential of mean force (PMF).

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