Binding site of Scorpion toxin HsTx1 to the potassium channel Kv1.1 and Kv1.3 from Molecular Dynamics simulations

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HsTx1 is a scorpion toxin belonging to the αKTx6 family. This 34-residue toxin cross linked between α helices and β sheet by four disulphide bridges. HsTx1 potently blocks Kv1.3 (11 pm) and Kv1.1 (7 nm) only. Here we explore the binding site of the toxin with voltage-gated potassium channel Kv1.1 and Kv1.3 from MD simulation which is a powerful tool in molecular level for understanding the electrophysiological experiments performed on wild-type and mutant channel. We dock the ligand in Kv1.1 and Kv1.3 homology model (from crystal structure of Kv1.2), using Haddock. Docked complexes are refined with MD simulations to find the interacting residues of HsTx1 with Kv1.1 and Kv1.3 channels. We have run the MD simulation up to 20 ns for the channel-toxin complex in a solvated lipid bilayer environment. This has confirmed that the toxin and the pore region of the channel are flexible in the binding. The last 15 ns is considered as the production time. Recognition residues and interaction contacts for the binding are identified during this time of simulation. Lys-23 goes far inside the channels. In HsTx1-Kv1.1 Arg4/Glu353(C), Thr5/Met378(C), Arg14/Glu353(B) and Arg33/Glu353(A) are involved in binding. Thr5/Met403(C), P6/His404(B), Lys7/Asp376(B), Tyr21/Asp402(B) Met25/H404(D) Asn26/Asp402(D) and Arg33/Glu373(A) are the interacting residue pairs in the HsTx1-Kv1.3 complex. We calculate the potential of mean force(PMF) of its unbinding from the channel to compare with experimental result and validate the complex. The consistency between the result of the simulations and the experimental data indicates that our three-dimensional models of the toxin-channel complex are reasonably accurate. So our model can be used as a guide for future biological studies, to improve the selectivity of other toxins such as ShK in Kv1.3. Here we propose mutation R14A to increase the selectivity.