Thumbs up for PcTx1 – mechanistic insight into the binding of the venom peptide PcTx1 to the acid sensing ion channel 1a from free energy calculations

E. Deplazes,[1,2,3] M. Stroet,[2] G.F. King[3] and A.E. Mark,[2,3] [1]School of Biomedical Sciences, Curtin University, Perth, WA 6109, Australia, [2]School of Chemistry & Molecular Biosciences, The University of Queensland, St Lucia, QLD 4072, Australia and [3]Institute for Molecular Bioscience, The University of Queensland, St Lucia, QLD 4072, Australia.

The acid sensing ion channel 1a (ASIC1a) is a proton-gated channel involved in many physiological processes and a drug target for treating neurological disorder and pain. PcTx1, a 40-residue peptide isolated from the venom of the tarantula Psalma cabridgei, is the most potent selective inhibitor of ASIC1a. Recent crystal structures of the ASIC1a-PcTx1 complex have revealed an extensive network of peptide-channel contacts. Our subsequent study combining simulations and mutagenesis of the peptide and the channel revealed that only a subset of the many contacts in the ASIC1a-PcTx1 crystal structure are critical for PcTx1 activity, thus defining the main pharmacophore of PcTx1. Despite the large amount of structural and functional information on the binding of PcTx1 to ASIC1a, little is known about the thermodynamics and pathway of binding.

In this study we use free energy calculations as well as unrestrained MD simulations of the apo channel and the ASIC1a-PcTx1 complex to investigate the binding of PcTx1 to ASIC1a at atomistic resolution. The free energy calculations predict a binding free energy (ΔG) of –52 kJ/mol, which is in very good agreement with experimental binding affinities. The simulations reveal that binding of PcTx1 is a highly dynamic, two-state process that involves formation of transient interactions and previously unseen conformational changes in the channel. Furthermore, the simulations revealed that the binding of a single peptide induces the same conformational changes in all three subunits of the channel indicating that the binding of PcTx1 is cooperative. This investigation represents the first extensive simulation study of a peptide-ASIC complex and provides new mechanistic insight into the binding of PcTx1 that is likely relevant to the binding of other venom peptides to ASIC1a. As part of this study we have also developed a freely available Python implementation of the UI method that include error analysis and convergence checks.