Modeling and Molecular Dynamic Simulations of Calcium Channel Voltage Sensor

Stefania Monteleone[1], Julian E. Fuchs[1], Alexandra Pinggera[2], Petronel Tuluc[2], Jörg Striessnig[2], Klaus R. Liedl[1]

[1] *Department of Theoretical Chemistry*

[2] *Department of Pharmacology and Toxicology*

University of Innsbruck, Innrain 80/82, 6020 Innsbruck, Austria

Voltage-gated calcium channels are involved in several diseases, but the investigation of their mechanisms needs an atomic-detailed study of the protein. Mutations in the pore forming α_1 subunit of $Ca_v1.3$ isoform have recently been shown to drive excess aldosterone secretion from aldosterone producing adenomas [1]. Since crystal structures of α_1 subunit are not yet available, we used molecular modeling to predict potential functional changes of one of the mutations in the voltage sensors.
Firstly, homology modeling of the activated state has been performed starting from the X-ray structure of a sodium channel as template [2], only to predict the transmembrane segments because of higher sequence similarity. At a later step, we used the ab initio Rosetta method to model intra- and extracellular loops, without any constraints [3]. The resting state has been modeled starting from the previous model: indeed, since there are no crystal structures for resting voltage sensors of ion channels, we edited the sequence alignment in order to get different matches of key charged residues in the voltage sensor.
Afterwards, models have been minimized in a periodic box including lipids, water molecules and ions, and through molecular dynamic simulations we investigated the most important interactions among charged residues in the resting and activated states.
Moreover, we analyzed the diffusion of water molecules in the voltage sensor in native and mutant proteins: in particular, the mutation of one arginine residue to histidine (R990H) resulted in the formation of a wire of water molecules in the resting state, that was not present in the wild-type protein. This might involve the development of omega-currents in the voltage sensor, that often cause ion channel related diseases [4].

References

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