Computer simulations as a tool for understanding ion channels function and regulation.

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Abstract

Pentameric ligand gated ion channels (pLGICs) are brain receptors involved in fast neurotransmission at synapses and include the nicotinic acetylcholine, the GABAA, the glycine or the serotonin receptors. pLGICs are present in eukaryotic and prokaryotic organisms with a surprising structural similarity. When dysfunctioning, they are involved in a number of diseases including Alzheimer's, Parkinson's, epilepsy, or certain types of schizophrenia. These ion channels can be activated or potentiated by orthosteric or allosteric ligands and are the pharmacological targets of commercially available drugs such as STROMECTOL or REMINYL. Nonetheless, their mechanism of action has remained elusive. In the past years, crystallographic studies in combination with electrophysiology and computer simulations based on molecular dynamics (MD) have provided important insight on the mechanism of signal transduction.

In this endeavor, the high resolution structure of a glutamate gated chloride channel (GluCl) which was the first eukaryotic channel ever solved in this family was crystallized in the presence of the endogenous neurotransmitter (glutamate) and the allosteric modulator, ivermectin (IVM). This structure is believed to represent an active state and was a breakthrough in the field. More recently a structure of GluCl with no ligand bound, i.e. apo GluCl, was solved by X-ray crystallography and is thought to represent a resting state.

Using these high resolution structures, we have performed a total of 6μs MD simulations of this pLGIC i) with IVM, ii) without IVM and iii) with no ligand. The removal of IVM captured the full closing transition from active to resting and provided a detailed mechanistic interpretation of ion gating. We used the simulations of GluCl bound to IVM and apo as references to asses for the validity of the transition.

Our analysis provides a time-resolved atomistic description of the gating mechanism which occurs in two steps : a global twisting of the receptor followed by a radial expansion of the upper domain resembling the blooming of a blossom. We believe this mechanism to be

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applicable to the whole pLGICs family.

In a second time, free energy calculations along the two isolated reaction coordinates for activation, i.e. blooming and twisting were performed for various ligand-protein complexes. Doing so we could show how small molecule binding may affect the conformational isomerization of the neurotransmitter receptor. Thus offering rational ways to explore new pharmacological strategies of ion-channel modulation.