Elucidating the Gating Mechanism of Cys-Loop Receptors

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Abstract

Cys-loop receptors are membrane proteins that are key players for the fast synaptic neurotransmission. Their ion transport initiates new nerve signals after activation by small agonist molecules, but this function is also highly sensitive to allosteric modulation by a number of compounds such as anesthetics, alcohol or anti-parasitic agents. For a long time, these modulators were believed to act primarily on the membrane, but the availability of high-resolution structures has made it possible to identify several binding sites in the transmembrane domains of the ion channels. It is known that ligand binding in the extracellular domain causes a conformational earthquake that interacts with the transmembrane domain, which leads to channel opening. The investigations carried out in this thesis aim at understanding the connection between ligand binding and channel opening.

I present new models of the mammalian GABA<sub>A</sub> receptor based on the eukaryotic structure GluCl co-crystallized with an anti-parasitic agent, and show how these models can be used to study receptor-modulator interactions. I also show how removal of the bound modulator leads to gradual closing of the channel in molecular dynamics simulations. In contrast, simulations of the receptor with both the agonist and the modulator remain stable in an open-like conformation. This makes it possible to extract several key interactions, and I propose mechanisms for how the extracellular domain motion is initiated.

The rapid increase in the number of cys-loop receptor structures the last few years has further made it possible to use principal component analysis (PCA) to create low-dimensional descriptions of the conformational landscape. By performing PCA on the crystal structure ensemble, I have been able to divide the structures into functional clusters and sample the transitions between them using various sampling methods.

The studies presented in this thesis contribute to our understanding of the gating mechanism and the functional clustering of the cys-loop receptor structures, which both are important to design new allosteric modulator drugs that influence the channel function, in particular to treat neurological disorders.

Key Words

ion channel, gating, simulation, molecular dynamics, receptor, cys-loop, modelling