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Gating and drug modulation in ligand-gated ion channels: Insights from X- ray crystallography and Cryo-EM

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The pentameric ligand gated ion channels (pLGICs) are belong to cys- loop superfamily. pLGICs are responsible for fast chemical transmission of nerve signals in the central and peripheral nervous system. These channels are expressed in the human brain and are modulated by large number of both endogenous and exogenous agents such as lipids, alcohol, anesthetics and neurosteroids. The binding of a neurotransmitter initiates a cascade of protein motions that leads to transitions between closed, open, and desensitized conformations. Ionic fluxes, and hence the post-synaptic responses, are critically governed by the transition rates and equilibrium populations of these functional states. Aberration of these molecular events underlies many neurological disorders and therefore, pLGICs are therapeutic targets for treating these conditions. The detailed molecular understanding of the gating mechanism and its modulation requires high-resolution structures of the channel in multiple functional states. While there has been ground-breaking progress in structural determination of several members of the pLGIC family (from both prokaryotic and eukaryotic origin), an unequivocal assignment of functional states to these conformations has not been achieved. Initially, we choose prokaryotic homologue, GLIC, a proton gated bacterial ion channel from *Gloeobacter violaceus*. GLIC has the overall similar structure as the family of ion channels, and are highly amenable to structural and functional studies in a native environment. I have utilized multidisciplinary approaches such as X-ray crystallography, two electrode voltage clamp, EPR spectroscopy to elucidate how GLIC is modulated by polyunsaturated fatty acid, DHA. Later, I have focused on more complex eukaryotic pLGIC, serotonin receptor (5-HT₃AR). 5-HT₃AR activities directly regulate gut movement and therefore drugs that inhibit 5-HT₃AR function are used to control vomiting reflexes. Serotonin binding induces a global conformational change encompassing the ligand-binding extracellular domain (ECD), the transmembrane domain (TMD), and the intracellular domain (ICD), the molecular details of which are unclear. I have solved the apo state as well as two serotonin bound structures of the full-length 5-HT₃AR in distinct conformations using cryo-EM that reveal the mechanism underlying channel activation. Recently, I solved high resolution structure of drugs (setrons) bound 5-HT₃AR structures which reveals the mechanism of antagonism. These studies will pave the way for design of drugs that specifically target the 5-HT₃R in the central nervous system or gut to treat psychiatric or gastrointestinal-tract-related conditions with less off-target effects.