New insights into structures of pentameric ligand-gated ion channels

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Pentameric ligand-gated ion channels (pLGICs), such as neuronal α7 nicotinic acetylcholine receptor (α7nAChR), are responsible for fast synaptic transmission and involved in cognitive functions and various neurological disorders, such as chronic pain, depression, and neuroinflammation. The diverse roles of pLGICs may be mediated in part by direct interaction with intracellular proteins involved in synaptic plasticity and downstream signaling pathways. Development of therapeutic strategies targeting specific human pLGICs, however, has been restrained partially by the lack of high-resolution structures of pLGICs and molecular details of pLGICs' interactions with intracellular proteins. Recently we have made a significant progress in the structural investigation of pLGICs using nuclear magnetic resonance and electron spin resonance spectroscopies, X-ray crystallography, and electron microscopy. Conformational changes of pLGICs have been revealed for different functional states and drug modulations. For α7nAChR in particular, the structural details starts to emerge, including the most mysterious intracellular domain of α7nAChR and its interaction protein partners. These studies advance the current understanding of pLGICs and lay the groundwork for the rational design of novel therapeutic strategies. The research is supported by NIH funding.