MEMBRANES & MOLECULES

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Allosteric transition of a bacterial pentameric ligand-gated ion channel

abstract

Pentameric channel-receptors, including nicotinic acetylcholine receptors, play a key role in fast excitatory and inhibitory transmission in the nervous system and are the target of numerous therapeutic and addictive drugs. They carry several neurotransmitter binding sites which govern the opening of a transmembrane ion channel. Extensively expressed in animals, they were found in several bacteria, especially the homolog from the cyanobacteria *Gloeobacter violaceus* (GLIC) which functions as a proton-gated ion channel. The simplified architecture of this archaic homologue, as well as its prokaryotic origin, allowed solving its X-ray structure in two closed and one open conformation. Those static structures suggest that channel opening occurs through symmetrical quaternary twist and "blooming" motions, together with tertiary deformation, according to a global transition that couples channel opening with reorganization of the binding pockets for neurotransmitters and allosteric effectors. To investigate the dynamics of the protein, we further engineered multiple fluorescent reporters, each incorporating a bimane and a tryptophan/tyrosine, whose close contact causes fluorescence quenching. We show that proton application causes a global compaction of the extracellular subunit interface, coupled to an outward motion of the M2-M3 loop near the channel gate, and that these movements are highly conserved in lipid vesicles and detergent micelles. Real-time recordings show that most structural reorganizations are completed within 2ms, much faster than channel opening. Our work thus identifies and structurally characterizes a new pre-active intermediate state in the transition pathway towards activation. Such pre-active state has been previously inferred from single-channel kinetic analysis of the muscle nAChR, and the present work provides for the first time a structure template of such short-lived state.

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