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Conformation changes in the Glutamate receptor as studied by LRET

VASANTHI JAYARAMAN, University of Texas Health Science Center at Houston

Glutamate receptors are the primary mediators of excitatory neurotransmission in the mammalian central nervous system. Glutamate binding to an extracellular ligand binding domain initiates a series of conformational changes that results in the formation of cation selective transmembrane ion channels that ultimately desensitize. We have used luminescence resonance energy transfer to determine the conformational changes that underlie the allosteric process of glutamate mediated gating in the receptor. These investigations showed that agonist binding induced cleft closure in the ligand binding domain confirming that this change observed in the isolated ligand binding domain of the receptor is one of the mechanisms by which agonist mediates activation. The LRET investigations also allowed a study of the conformational changes between the subunits. The apo state of the protein showed a dimer interface that was open. The dimer interface was brought together only in the activated state, suggesting that cleft closure drives the formation of the contacts at dimer interface, which in turn transiently stabilizes the open channel. At longer times, the stress induced by the transmembrane segments, ultimately drives the breakdown of the interface, leading to channel closure and receptor desensitization.