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Distinguished Lecture Series

Ligand-binding effects on the structure of the AMPA-glutamate receptor channel: A puzzling cryo-EM result



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Molecular Physiology,
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Time:

3:00 PM

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Venue:

RCB Campus

180, Udyog Vihar Phase 1
Gurgaon

The X-ray crystal structure of GluA2 AMPA-type glutamate receptors is known (Sobolevsky & Gouaux, Nature 2009), and we have been imaging the same receptors by cryo-EM. A 3D reconstruction from our images of antagonist-bound receptors matches very closely the corresponding crystal structure, in which the extracellular domains of the tetrameric receptors are bound together in a compact dimer-of-dimers arrangement. The processes of activation and desensitization of receptors are thought to be orderly conformational changes wherein the closure of the "clamshell" ligand-binding domains (LBDs) around bound glutamate molecules cause transmembrane helices to move about, opening or closing the channel "gate". However, our cryo-EM snapshots of functional receptors in the presence of glutamate show LBDs and extracellular amino-terminal domains which have dissociated from one another and are undergoing wild, flexible motions. The desensitization of the AMPA receptor, we reluctantly conclude, follows from the random motions of a very relaxed protein structure.