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#Co-corresponding

ABSTRACT Metabotropic glutamate receptors belong to a family of G protein-coupled receptors that are obligate dimers and possess a large extracellular ligand-binding domain that is linked via a cysteine-rich domain to their 7-transmembrane domain. Upon activation, these receptors undergo a large conformational change to transmit the ligand binding signal from the extracellular ligand-binding domain to the G protein-coupling 7-transmembrane domain. In this manuscript, we propose a model for a sequential, multistep activation mechanism of metabotropic glutamate receptor subtype 5. We present a series of structures in lipid nanodiscs, from inactive to fully active, including agonist-bound intermediate states. Further, using bulk and single-molecule fluorescence imaging, we reveal distinct receptor conformations upon allosteric modulator and G protein binding.

