STRUCTURAL BASIS OF THE HUMAN MGLU5 RECEPTOR ACTIVATION MECHANISM

G. LEBON [1]

[1] *IGF - Montpellier (France)*

Metabotropic glutamate receptors (mGluR) are Class C GPCRs. They are obligate dimers, dimerization being fundamental for their function. mGluRs are activated by the binding of the main excitatory neurotransmitter glutamate, within a large extracellular domain (ECD). Conformational changes induced by glutamate-binding are then transmitted to the transmembrane domain composed of 7 transmembrane helices (7TM) that allows signal transduction within the cell. Class C GPCR activity can also be modulated by the binding of Positive Allosteric Modulators (PAM) or Negative Allosteric Modulators (NAM) to the 7TM domain. As a first step toward structure determination of mGluRs, we have thermostabilised the mGlu5 receptor that retains the capability to activate the G protein. Using single particle electron cryomicroscopy (cryoEM), we have solved the structure of the inactive conformation of receptor bound to an antagonist and to a NAM, as well as the intermediate-active agonist and PAM-bound state. In parallel, we solved a high-resolution structure of the thermostabilised 7TM bound to photoswitchable NAM, by using X-ray crystallography. Molecular details of mGlu5 receptor activation mechanism were further investigated by performing a structure-function analysis of alanine mutants of the mGlu5 receptor coupled to photopharmacology. Structures of the human mGlu5 receptor will be presented and the structural basis of the receptor dimer activation mechanism will be discussed.