Domain Closure of the Ligand-binding Core of the AMPA Receptor GluR2: Insights from Agonist and Antagonist Complexes

Christina Kasper, Karla Frydenvang, Bente Vestergaard, Desiree Sprogøe, Helle Hald, Lotte Brehm, Michael Gajhede, Jette Sandholm Kastrup, *Biostructural Research, Department of Medicinal Chemistry, Danish University of Pharmaceutical Sciences, Denmark.* E-mail: jsk@dfuni.dk

Ionotropic glutamate receptors (iGluRs) mediate most rapid excitatory synaptic transmission in the mammalian central nervous system and their involvement in neurological diseases has stimulated widespread interest in their structure and function.

We have determined several structures of a ligand-binding core construct of GluR2 (GluR2-S1S2J), which belongs to the AMPA class of iGluRs, in complex with agonists and antagonists. GluR2-S1S2J is composed of two domains (D1 and D2) and the ligands bind within a cleft formed by the domains. AMPA receptor agonists induce distinct conformations of the GluR2-S1S2J by D1-D2 domain closure. In contrast, antagonists stabilize an open conformation of GluR2-S1S2J, resembling the conformation of the *apo* structure.

An excellent correlation exists between domain closure and efficacy of a range of agonists at full-length GluR2, determined by electrophysiology in *Xenopus lævis* oocytes. Together with the various binding modes of agonists and antagonists at GluR2-S1S2J, this will be discussed on the poster.

[1] Frandsen A., Pickering D.S., Vestergaard B., Kasper C., Nielsen B.B., Greenwood J.R., Campiani G., Fattorusso C., Gajhede M., Schousboe A., Kastrup J.S., *Mol. Pharmacol*., 2005, **67**, 703.

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