CRYSTALLOGRAPHIC STUDY OF THE METABOTROPIC GLUTAMATE RECEPTOR

The metabotropic glutamate receptor (mGluR) is a key membrane receptor involved in the modulation of excitatory synaptic transmission in the central nervous system. The mGluR plays a crucial role in learning, memory, and some mental disorders, and is therefore a major target for drug-design. To elucidate the mechanism in which ligand-binding triggers the activation of the receptor, we have analyzed the extracellular ligand-binding region of mGluR1 (m1-LBR) using X-ray crystallography [1].

Three different crystal structures of m1-LBR have been determined in a complex with glutamate and in two non-ligand forms. The diffraction data was collected at two beamlines, **BL45XU** (complex form) and **BL24XU** (free forms). For phase determination, we applied the multi-wavelength anomalous diffraction (MAD) method using the facilities at BL45XU. The crystal structures of all the three forms exhibit disulfide-linked homodimers, where “active” and “resting” conformations are modulated through the novel dimeric interface by a packed alpha-helical structure (Fig. 1). The interprotomer disulfide bridge [2] most likely functions as an interprotomer linker which increases the effective concentration of a dimeric form of mGluR1 on the cellular surface. Each protomer consists of two domains: designated as LB1 and LB2. Glutamate is bound in an interdomain crevice (Fig. 2). The differing interdomain arrangements provide an “open” or “closed” conformation of the bi-lobed protomer.

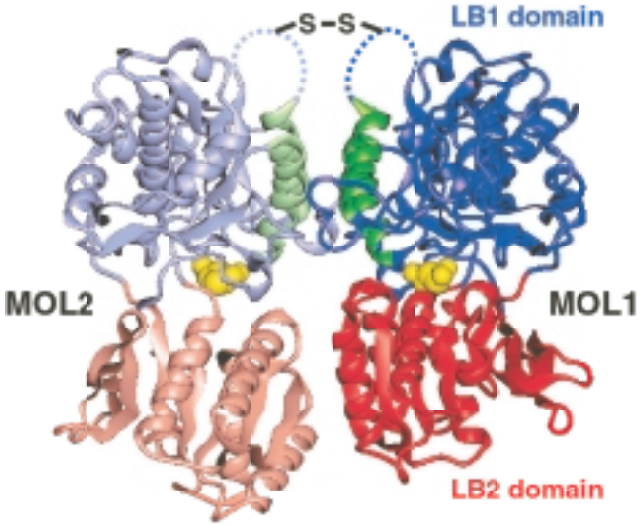

*Fig. 1. Crystal structure of m1-LBR dimer in the glutamate complex form. The MOL1 and MOL2 molecules in the dimer are distinguished by dark and light coloring, respectively. Bound glutamate molecules are shown as yellow space-filling models. Disordered regions with a potential interprotomer disulfide bridge are indicated by dotted lines. Helices **B** and **C**, constituting the dimer interface, are colored green.*

These structures imply that glutamate binding stabilizes both the “active” dimer and “closed” protomer in dynamic equilibrium. The movements of the four domains within the dimer are likely to affect the separation of the transmembrane and intracellular regions, and thereby glutamates with a small molecular size activate the receptor (Fig. 3). This scheme for initial receptor activation could be applied generally to G-protein-coupled neurotransmitter receptors which possess extracellular ligand binding sites.

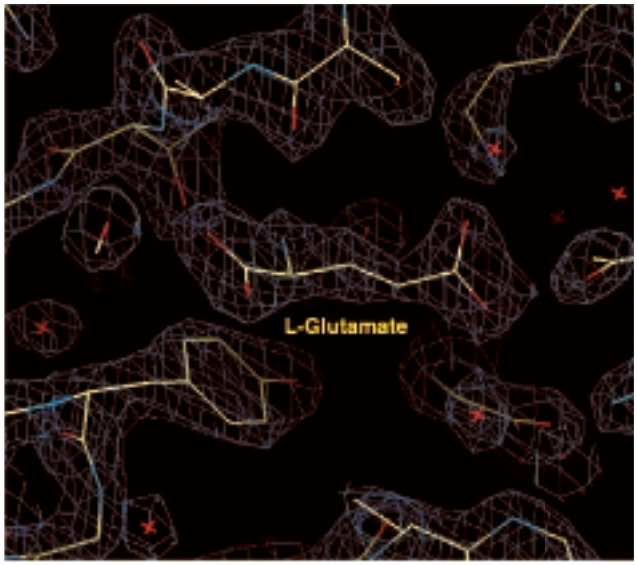

Fig. 2. Final 2Fo-Fc electron density map around the glutamate binding site at 2.2 Å resolution.

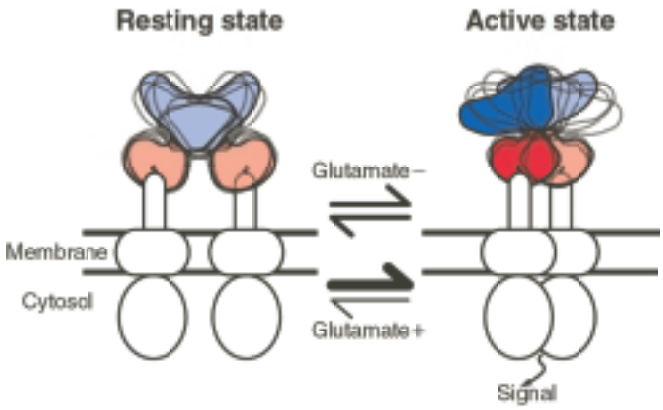

Fig. 3. Potential activation mechanism of mGluR1. The two observed conformations of m1-LBR are represented by solid lines with colors. Open and closed conformations are distinguished by light and dark coloring, respectively. Other unidentified conformations of m1-LBR are indicated by dotted lines. Remaining regions not determined in this study are shown schematically.

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References

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