Learning from rhodopsin about metabotropic glutamate receptors

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Metabotropic glutamate receptors (mGluRs) are G protein coupled receptors that play important roles in synaptic plasticity and other neuro-physiological and pathological processes. Allosteric mGluR ligands are particularly promising drug targets because of their modulatory effects--enhancing or suppressing the response of mGluRs to glutamate. The mechanism by which this modulation occurs is not known. We have proposed the hypothesis that positive and negative modulators will differentially stabilize the active and inactive conformations of the receptors, respectively [1]. To test this hypothesis, we have generated computational models of the transmembrane regions of different mGluR subtypes in two different conformations. The inactive conformation was modeled using the crystal structure of the inactive, dark state of rhodopsin as template and the active conformation was created based on a recent model of the light-activated state of rhodopsin. Ligands for which the nature of their allosteric effects on mGluRs is experimentally known were docked to the modeled mGluR structures using ArgusLab and Autodock softwares. We find that the allosteric ligand binding pockets of mGluRs are overlapping with the retinal binding pocket of rhodopsin, and that ligands have strong preferences for the active and inactive states depending on their modulatory nature. These findings support the hypothesis that mGluR allosteric modulation occurs via stabilization of different conformations analogous to those identified in rhodopsin where they are induced by photochemical isomerization of the retinal ligand--despite the extensive differences in sequences between mGluRs and rhodopsin. Correlated mutation analysis of mGluR and rhodopsin sequences suggests that long-range allosteric communication is conserved in general but differs in the specific areas of the proteins that are linked. We are in the process of testing the generality between rhodopsin and mGluRs experimentally and have developed an expression and purification system for mGluR type 6. This receptor is only expressed in ON-bipolar cells and is implicated in night blindness and drug addiction. Preliminary biophysical studies on (mis)folding and protein structure will be presented.

[1] Yanamala, N., Tirupula, K.C. and Klein-Seetharaman, J. (2008) Preferential binding of allosteric modulators to active and inactive conformational states of metabotropic glutamate receptors. BMC Bioinformatics 9, Suppl 1:S16.