Metabotropic Glutamate Receptors: complex allosteric machines offering many possibilities for new drugs

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G protein-coupled receptors play key roles in cell-cell communication processes, and, not surprisingly, are the main targets for therapeutic drugs. These receptors are the target of many different signaling molecules, including the main excitatory neurotransmitter, glutamate. Although the later exerts its fast excitatory actions through ligand-gated channels –i.e. the NMDA, AMPA and kainate receptors - it also acts on GPCRs called metabotropic glutamate receptors (mGluRs) to modulate synaptic activity. There are eight genes encoding such receptors and classified in three groups. While group-I (mGlu1 and 5) regulate synaptic activity at the post-synaptic level, both group-II (mGlu2 and 3) and group-III (mGlu4, 7 and 8) are pre-synaptic receptors (the group-III receptor mGlu6 is specifically expressed in On bipolar cells, receiving the information from the photoreceptor cells). Not surprisingly, these receptors offer a number of possibilities to develop new therapeutic drugs for the treatment of various neurological and psychiatric diseases.

The mGluRs are much more complex proteins compared to other GPCRs. They are made of two subunits covalently linked by a disulfide bridge, each being composed of a venus flytrop domain (VFT) where glutamate binds, connected via a cystein-rich domain to a heptahelical membrane domain responsible for G protein activation. Such a large protein complex undergoes major conformational changes upon ligand binding in the VFT, leading to the activation of one 7TM domain.

During this presentation, I will summarize our view of the activation mechanism of these receptors, and illustrate the multiple possibilities offered to develop innovative molecule able to specifically regulate them. These include orthosteric as well as allosteric compounds, including antibodies that can be design to specifically target such receptors and better identify their therapeutic potential.