# Activation Routes of G-Protein-Coupled Receptors

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G protein coupled receptors (GPCRs), also called 7TM receptors from seven transmembrane domains, form a huge superfamily of membrane proteins that, upon activation by extracellular signals, physical or chemical, pass the signal to the cell interior. More than 800 human GPCRs allow cells to recognize diverse extracellular stimuli (photons, odorants, hormones, lipids, neurotransmitters, etc.) and transduce the signals across the plasma membrane to regulate essential physiological processes. Upon activation they pass the signal to the mediating proteins which is G protein but also arrestin. Family of GPCRs is a major class of membrane signaling proteins so these receptors are pharmacological targets for over 30% of currently used drugs.

At present, the structures of about 20 different types of GPCRs are known due to progress in micro-crystallography and in mutational thermal stabilization of these proteins. However, details of the structural and dynamical transitions within the receptors during transmembrane signaling are still unknown. The process of receptor activation consists of actions of so-called molecular switches buried in the receptor structure [1] and can lead to a wide range of activated or semi-activated structures depending on ligand bound.

We performed molecular dynamics studies of several GPCRs including N-formyl-peptide receptor (FPR1) [2], lipid receptor S1P1 [3] and μ-opioid receptor (μOR) [4]. We found that the extracellular pocket of FPR1 can be divided into two zones, namely, the anchor and activation regions. A mechanism was proposed concerning the initial steps of FPR1 activation concurrent with ligand binding. For FPR1 and S1P1 it was found that water molecules entering the receptor upon agonist binding are necessary for subsequent activation states. For μOR the MD simulations resolved the experimentally found dual role of sodium ions (i) to decrease the binding affinity for agonists, and (ii) to facilitate G protein activation. Sodium ions can facilitate the activation of μOR by inducing the movement of water molecules towards the allosteric site which influence an action of the orthosteric agonist. We also developed a GPCRM server [5] for construction of homology models of GPCRs that can be used for activity studies and also drug design purposes.

**References:**

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