1-SL03 Special Lecture3

The activation mechanism and drug discovery of G protein-coupled receptor

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More than 800 human GPCRs allow the selective detection of extracellular signals as diverse as photons, odorants, flavors, nucleotides, hormones, neurotransmitters – revealing GPCRs fundamental role in signal transduction. As they regulate many central physiological processes and are thus implicated in many diseases, GPCRs are among the most important targets for modern medicines. In spite of this medical importance and the recent progress in elucidating the 3D structures of various GPCRs, central questions how these receptors recognize extracellular chemical signals and transfer them across the cellular membrane to finally evoke an intracellular response are largely unresolved at a molecular level, mainly because the different steps during signal transmission are not directly accessible by experiments. In this context we are concentrating on central questions of GPCR mediated cellular signalling using computer based molecular dynamics simulations. Our work revealed for the first time, in atomic detail, the entire process of transmembrane signalling of various GPCRs: we found that ligand binding induces a series of conformational changes within a GPCR which opened a gate inside the receptor for water molecules entering the internal region of the receptor and subsequently driving conformational switches within the receptor which finally led to the activation of a G protein on the intracellular side of the receptor. We have applied our findings successfully to various GPCR targeted drug discovery projects.