Structure of rhodopsin mutants that constitutively activate the receptor

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G-protein coupled receptors are regulating every aspect of our human existence. They link us with visual perception, smell, taste to our environment and they control our mental state, happiness and consciousness. A drogue like LSD will change our mental state and our perception of the world. LSD is acting mainly over G- protein coupled receptors. More then 70 structures of 15 different GPCRs have determined in complex with ligands of varied pharmacology. From this we are able to extract important molecular signatures of G protein coupled receptor signaling. We have studied the structure of the β1 adrenergic receptor in several crystal forms and with several ligands. This provides important insights into ligand selectivity based on activation of the receptor and G protein activation. The third intracellular loop which is important for G protein activation is now resolved in several of our structures and shows two distinct confirmations. We now for the first time have observed a conformation of the fully inactivated receptor. The comparison of different loop conformations is allowing us to give a possible molecular explanation for the phenomenon of basal activity of GPCRs. The new structures also suggest a mechanism for a number of constitutively activating mutants. In addition this is very important for understanding the concept of inverse agonists and partial agonists in a molecular way. We have resolved several structures of constitutively active rhodopsin in an active confirmation with its natural agnostic retinal bound to the receptor. These structures give excellent insight into the activation mechanism of GPCRs and can explain some of the complex signaling behavior of G Protein Coupled Receptors.

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