Role of structural dynamics for GPCR signaling

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G Protein coupled receptors (GPCRs) are one of the most heavily investigated drug targets in the pharmaceutical industry covering different pathological areas including cancer, cardiovascular disorders, diabetes, central nervous system disorders, obesity, inflammation, and pain. A present key interest of the pharmaceutical industry is to design GPCR-targeted drugs with improved specificity and reduced side effects. This is challenging as one and the same receptor can activate different intracellular downstream signalling proteins such as heterotrimeric G proteins (Gαβγ; α-families Gi, Gs, Gq, G12/13) or arrestins (arrestin 1−4), resulting in different (either wanted or unwanted) cellular and physiological responses. Understanding the molecular mechanism of this coupling promiscuity is thus a major question in current receptor research.

I will summarize our attempts to elucidate coupling specificity in G protein coupled receptor signalling using molecular dynamics simulations referencing related experimental work. According to our knowledge based concept, structural flexibility plays a key role in specific recognition and binding of G proteins to active receptors. Our concept of receptor G protein coupling specificity may pave the way for novel concepts and approaches to develop drugs with limited side effects. Computer simulations are available through web-services developed in my laboratory using innovative approaches for interactive visualisation of even huge amounts of data.