

Influence of New High-Resolution Structures and Oligomerization on Molecular Modeling and Simulations of G-Protein Coupled Receptors.

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For several years inactive bovine rhodopsin has been the only GPCR of known crystallographic structure, thus serving as the most reliable template for homology modeling and simulations of other GPCRs. Recently, the crystal structures of inverse agonist-bound GPCRs from three different species have been determined: squid rhodopsin, beta2 adrenergic, and beta1 adrenergic receptors. These findings, together with the novel crystal structure of ligand-free native bovine opsin, which encompasses some of the structural changes that were attributed to active GPCR states, have shed new light on ligand binding to GPCRs and on GPCR activation. However, the increasingly supported role of oligomerization in GPCR function, recently enriched with novel biophysical results, complicates the already challenging goal of unraveling the molecular mechanisms of these receptors. We are using current structural and biophysical knowledge to elucidate allosteric dynamics and functional selectivity of GPCRs by means of modern molecular models and fast molecular dynamics approaches.