Theoretical study on receptor-G protein recognition

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The rhodopsin family of receptors employs guanine nucleotide binding proteins (G proteins) to transduce signals across the cell membrane. All these receptors share the presence of seven hydrophobic regions that are believed to form a bundle of a-helical transmembrane domains connected by alternating intracellular and extracellular hydrophilic loops. The G proteins consist of three subunits a, b and g. In the inactive state, G proteins form membrane-associated abg heterotrimers, with GDP tightly bound to the a subunit. Upon activation by extracellular signals, the receptors catalyze the exchange of bound GDP for GTP promoting a variety of intracellular biochemical events. Despite the fact that recent crystallographic studies of G protein a subunits and heterotrimers have begun to show how G proteins might work, a consistent description of the mechanisms of receptor activation as well as of receptor catalyzed nucleotide exchange in terms of both structure and dynamics still remains a daunting task. One obvious problem is the lack of the high resolution structure of G protein coupled receptors (GPCRs).
Recently, we used all the experimental information available on GPCRs for building a 3D model of the Gaq coupled a1b-adrenergic receptor (a1b-AR) and employed a combined experimental and Molecular Dynamics (MD) simulated mutagenesis approach to investigate the activation mechanism of this receptor [1-3]. These studies suggested that the highly conserved polar amino acids in the seven-helix bundle play a fundamental structural role, driving the motion of the helices which culminate into a rearrangement of the cytosolic domains that are involved in receptor/G-protein recognition. The mutation- and agonist-induced active states of the receptor share several structural peculiarities including: a) the release of some constraining interactions found in the wild type receptor and/or in its inactive mutants and b) the opening of a cytosolic site formed by i2, i3 and the cytosolic extension of helices 5 and 6. New insights into the mechanism of receptor activation were gained by simulating the association between several active forms of the a1b-AR and the GDP-bound Gaqb1g2 heterotrimer [4], by means of automatic rigid body docking [5]. The results of this study provided useful suggestions about the potential receptor-G-protein interface. The same approach was also employed to investigate the domains involved in receptor homodimerization [4] as well as the molecular determinants of receptor/G protein specificity [6].

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