Theoretical study on mutation-induced activation of GPCRS

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The rhodopsin family of receptors employs guanine nucleotide binding proteins (G proteins) to transduce signals across the cell membrane. All the G protein coupled receptors (GPCRs) share the presence of seven hydrophobic regions that are believed to form a bundle of α-helical transmembrane domains connected by alternating intracellular and extracellular hydrophilic loops. Three-dimensional model building and molecular dynamics (MD) simulations of the α1b-adrenergic receptor (α1b-AR), of the oxytocin receptor (OTR) and of the luteinizing hormone receptor (LHR) were employed to provide hypotheses about the molecular mechanisms underlying the mutation-induced activation of these GPCRs. (1-6) The comparative analysis of the wild type receptors and of several constitutively active or inactive mutants was instrumental to infer the structural/dynamics features which could characterize the active and the inactive forms of these receptors. These features were also employed for predicting the functional behavior of new receptor mutants.

Rigid body docking simulations between the functionally different forms of the α1b-AR and the LHR, on one hand, and heterotrimeric G proteins, on the other, suggested that the cytosolic crevice shared by the constitutively active receptor structures and formed by the second and the third intracellular loops as well as by the cytosolic extensions of helices 3, 5 and 6, might participate to receptor-G protein interface.

The results of this study might provide a structural framework to interpret the pathological effects induced by naturally occurring mutations of the LHR. In addition, the theoretical models here proposed can be useful for designing new mutations or ligands able to modulate receptor function as well as to drive experiments aimed at exploring the receptor-G protein interface.

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