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Study of Functional Relevant Conformational Mobility of β-2 Adrenoreceptor by Means of Molecular Dynamics Simulation

Authors : G. V. Novikov, V. S. Sivozhelezov, S. S. Kolesnikov, K. V. Shaitan

Abstract : The study reports about the influence of binding of orthosteric ligands as well as point mutations on the conformational dynamics of β-2-adrenoreceptor. Using molecular dynamics simulation we found that there was a little fraction of active states of the receptor in its apo (ligand free) ensemble corresponded to its constitutive activity. Analysis of MD trajectories indicated that such spontaneous activation of the receptor is accompanied by the motion in intracellular part of its alpha-helices. Thus receptor's constitutive activity directly results from its conformational dynamics. On the other hand the binding of a full agonist resulted in a significant shift of the initial equilibrium towards its active state. Finally, the binding of the inverse agonist stabilized the receptor in its inactive state. It is likely that the binding of inverse agonists might be a universal way of constitutive activity inhibition in vivo. Our results indicate that ligand binding redistribute pre-existing conformational degrees of freedom (in accordance to the Monod-Wyman-Changeux-Model) of the receptor rather than cause induced fit in it. Therefore, the ensemble of biologically relevant receptor conformations is encoded in its spatial structure, and individual conformations from that ensemble might be used by the cell in conformity with the physiological behaviour.

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