Backbone NMR reveals allosteric signal transduction networks in the β1-adrenergic receptor

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G protein-coupled receptors (GPCRs) are physiologically important transmembrane signalling proteins that trigger intracellular responses upon binding of extracellular ligands. Despite recent breakthroughs in GPCR crystallography, the details of ligand-induced signal transduction are not well understood owing to missing dynamical information. In principle, such information can be provided by NMR, but so far only limited data of functional relevance on few side-chain sites of eukaryotic GPCRs have been obtained. Here we show that receptor motions can be followed at virtually any backbone site in a thermostabilized mutant of the turkey β1-adrenergic receptor (β1AR). Labelling with [(15)N]valine in a eukaryotic expression system provides over twenty resolved resonances that report on structure and dynamics in six ligand complexes and the apo form. The response to the various ligands is heterogeneous in the vicinity of the binding pocket, but gets transformed into a homogeneous readout at the intracellular side of helix 5 (TM5), which correlates linearly with ligand efficacy for the G protein pathway. The effect of several pertinent, thermostabilizing point mutations was assessed by reverting them to the native sequence. Whereas the response to ligands remains largely unchanged, binding of the G protein mimetic nanobody NB80 and G protein activation are only observed when two conserved tyrosines (Y227 and Y343) are restored. Binding of NB80 leads to very strong spectral changes throughout the receptor, including the extracellular ligand entrance pocket. This indicates that even the fully thermostabilized receptor undergoes activating motions in TM5, but that the fully active state is only reached in presence of Y227 and Y343 by stabilization with a G protein-like partner. The combined analysis of chemical shift changes from the point mutations and ligand responses identifies crucial connections in the allosteric activation pathway, and presents a general experimental method to delineate signal transmission networks at high resolution in GPCRs.

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