Structure and dynamics determine G protein coupling specificity at a class A GPCR

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G protein coupled receptors (GPCRs) exhibit varying degrees of selectivity for different G protein isoforms. Despite the abundant structures of GPCR-G protein complexes, little is known about the mechanism of G protein coupling specificity. The β_2-adrenergic receptor is an example of GPCR with high selectivity for Gαs, the stimulatory G protein for adenylyl cyclase, and much weaker for the Gαifamily of G proteins inhibiting adenylyl cyclase. By developing a Gαi-biased agonist (LM189), we provide structural and biophysical evidence supporting that distinct conformations at ICL2 and TM6 are required for coupling of the different G protein subtypes Gαs and Gαi. These results deepen our understanding of G protein specificity and bias and can accelerate the design of ligands that select for preferred signaling pathways.