Molecular insights into G-protein specificity and biased agonism at the β2-adrenergic receptor

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G protein coupled receptors (GPCRs) activated by their native hormone or neurotransmitter exhibit varying degrees of selectivity for different G protein isoforms. Despite the abundant structures of different GPCR-G protein complexes, little is known about the mechanism of G protein coupling specificity. There are a growing number of examples of pathway-selective or biased synthetic agonists that alter the G protein coupling preference for specific GPCRs. The β2AR is an example of a GPCR with high selectivity for coupling to Gαs, the stimulatory G protein for adenylyl cyclase, and much weaker for the Gi family of G proteins that inhibit adenylyl cyclase. While the Gαs pathway is the major therapeutic target for β2AR agonists, β2ARs have been shown to couple to Gαi isoforms in the heart, and this Gαi signaling may have relevance in the pathogenesis of heart failure. Here we present a new Gαi-biased agonist (LM189) for Gαi activation by the β2AR. We provide structural and biophysical evidence that the Gαi bias of LM189 can be attributed to an alteration in the structure and dynamics of ICL2 and TM6.