

Molecular insights into G-protein specificity and biased agonism at the β 2-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 β 2AR is an example of a GPCR with high selectivity for coupling to *Gas*, the stimulatory G protein for adenylyl cyclase, and much weaker for the *Gi* family of G proteins that inhibit adenylyl cyclase. While the *Gas* pathway is the major therapeutic target for β 2AR agonists, β 2ARs have been shown to couple to *G α i* isoforms in the heart, and this *G α i* signaling may have relevance in the pathogenesis of heart failure. Here we present a new *G α i*-biased agonist (LM189) for *G α i* activation by the β 2AR. We provide structural and biophysical evidence that the *G α i* bias of LM189 can be attributed to an alteration in the structure and dynamics of ICL2 and TM6.