

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 $G_{\alpha s}$, the stimulatory G protein for adenylyl cyclase, and much weaker for the G_i family of G proteins that inhibit adenylyl cyclase. While the $G_{\alpha s}$ pathway is the major therapeutic target for β 2AR agonists, β 2ARs have been shown to couple to $G_{\alpha i}$ isoforms in the heart, and this $G_{\alpha i}$ signaling may have relevance in the pathogenesis of heart failure. Here we present a new $G_{\alpha i}$ -biased agonist (LM189) for $G_{\alpha i}$ activation by the β 2AR. We provide structural and biophysical evidence that the $G_{\alpha i}$ bias of LM189 can be attributed to an alteration in the structure and dynamics of ICL2 and TM6.