

# Structural insights into differences in G protein activation by family A and family B GPCRs

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**ABSTRACT** Family B heterotrimeric guanine nucleotide-binding protein (G protein)-coupled receptors (GPCRs) play important roles in carbohydrate metabolism. Recent structures of family B GPCR-Gs protein complexes reveal a disruption in the  $\alpha$ -helix of transmembrane segment 6 (TM6) not observed in family A GPCRs. To investigate the functional impact of this structural difference, we compared the structure and function of the glucagon receptor (GCGR; family B) with the  $\beta_2$  adrenergic receptor ( $\beta_2$ AR; family A). We determined the structure of the GCGR-Gs complex by means of cryo-electron microscopy at 3.1-angstrom resolution. This structure shows the distinct break in TM6. Guanosine triphosphate (GTP) turnover, guanosine diphosphate release, GTP binding, and G protein dissociation studies revealed much slower rates for G protein activation by the GCGR compared with the  $\beta_2$ AR. Fluorescence and double electron-electron resonance studies suggest that this difference is due to the inability of agonist alone to induce a detectable outward movement of the cytoplasmic end of TM6.

