Allosteric interactions between GB1 and GB2 subunits are required for optimal GABA(B) receptor function

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Recent studies on G-protein-coupled receptors revealed that they can dimerize. However, the role of each subunit in the activation process remains unclear. The gamma-amino-n-butyric acid type B (GABA(B)) receptor is comprised of two subunits: GB1 and GB2. Both consist of an extracellular domain (ECD) and a heptahelical domain composed of seven transmembrane alpha-helices, loops and the C-terminus (HD). Whereas GB1 ECD plays a critical role in ligand binding, GB2 is required not only to target GB1 subunit to the cell surface but also for receptor activation. Here, by analysing chimeric GB subunits, we show that only GB2 HD contains the determinants required for G-protein signalling. However, the HD of GB1 improves coupling efficacy. Conversely, although GB1 ECD is sufficient to bind GABA(B) ligands, the ECD of GB2 increases the agonist affinity on GB1, and is necessary for agonist activation of the receptor. These data indicate that multiple allosteric interactions between the two subunits are required for wild-type functioning of the GABA(B) receptor and highlight further the importance of the dimerization process in GPCR activation.

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