Ligand-Dependent Distinct Coupling with G Proteins

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G proteins are classified into four families: G_s, G_i, G_q, and G_{12}. So far, β_2-adrenergic receptor (β_2AR)-mediated responses are believed to be exclusively mediated by G_s-adenylyl cyclase-cAMP pathway. However, it has been recently proposed that several G protein-coupled receptors transduce distinct signaling pathways through different G protein(s) in an agonist-dependent manner. We examined the possibility that β_2AR also couples to different G proteins. Among β_2-selective agonists, an order of efficacy to couple to G_s is isoproterenol > formoterol, procaterol > fenoterol >> salmeterol. These agonists also activated G_i, and an order of efficacy for β_2AR-G_i-coupling was same as that of β_2AR-G_s-coupling. We next examined whether β_2AR couples to G_{12} family G proteins, and found that β_2AR did not couple to G_{12} and G_{13}. β_2AR does not couple to G_q, but couples to G_{16}, a member of G_q family G protein. We found that β_2-selective agonists activated G_{16}, but the ability to activate G_{16} did not correlate with that of G_s. Therefore, the mode of β_2AR-G_{16} coupling is different from that of β_2AR-G_s coupling. We also examined the ability of β_2-selective agonists to activate β_1AR. In contrast to β_2AR activation, the agonist's ability to activate β_1AR was not correlated with that of β_2AR. It suggests that the amino acid residues of β_1AR which is necessary for the activation are different from that of β_2AR. Although β_2AR has an ability to couple to different G proteins, it remains that these results are translated into clinical significance.