

Structure of a Signaling Cannabinoid Receptor 1-G Protein Complex

Krishna Kumar K, Shalev-Benami M, Robertson MJ, Hu H, Banister SD, Hollingsworth SA, Latorraca NR, Kato HE, Hilger D, Maeda S, Weis WI, Farrens DL, Dror RO, Malhotra SV, Kobilka BK, Skinotitis G.

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ABSTRACT Cannabis elicits its mood-enhancing and analgesic effects through the cannabinoid receptor 1 (CB1), a G protein coupled receptor (GPCR) that signals primarily through the adenylyl cyclase-inhibiting heterotrimeric G protein G_i . Activation of CB1- G_i signaling pathways holds potential for treating a number of neurological disorders, and is thus crucial to understand the mechanism of G_i activation by CB1. Here we present the structure of the CB1- G_i signaling complex bound to the highly potent agonist MDMB-Fubinaca (FUB), a recently emerged illicit synthetic cannabinoid infused in street drugs that have been associated with numerous overdoses and fatalities. The structure illustrates how FUB stabilizes the receptor in an active state to facilitate nucleotide exchange in G_i . The results compose the structural framework to explain CB1 activation by different classes of ligands and provide insights into the G protein coupling and selectivity mechanisms adopted by the receptor.

