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Meeting abstract

Characterization of different G protein coupling properties of CB_1 and CB_2 cannabinoid receptors and GPR55 receptor using BRET

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Background

CB_1 and CB_2 cannabinoid receptors are G protein-coupled receptors which have been described to couple mainly to the $G_{i/o}$ subfamily of G proteins. However, in some cell types and upon stimulation with certain cannabinoid agonists, activation of other G protein subtypes has also been observed. GPR55 is an orphan G protein-coupled receptor which has been suggested to be a novel member of the cannabinoid receptor family.

Methods

In this study we wanted to characterize the G protein activation properties of the two known cannabinoid receptors and GPR55 following stimulation with different cannabinoid ligands, using bioluminescence resonance energy transfer (BRET). We monitored the activation of different G protein subtypes (G_o, G_q, G_s or G_{12}) using *Renilla* luciferase-tagged wild type or chimeric $G\alpha_o$ subunits (i.e. $G\alpha_o$ with the C-terminal 5 amino acids replaced with those of $G\alpha_q$, $G\alpha_s$ or $G\alpha_{12}$, respectively) co-expressed with EYFP-tagged $\alpha_1\alpha_{11}$ subunit and the receptor in CHO cells.

Results

We found that CB_1 was able to activate all four subtypes of G proteins, with different pharmacokinetic properties, following stimulation by non-selective (WIN55 and 2-AG) or CB_1-selective (ACEA) cannabinoid agonists. Basal activity of CB_1 could also be detected with G_o and G_{12} subtypes, as the CB_1 inverse agonist AM251 caused significant BRET increase (i.e. G protein subunit association) when tested with these G proteins. In contrast, CB_2 showed no G protein activation other than G_o, upon either WIN55 or 2-AG stimuli. Stimulation of GPR55 with WIN55, 2-AG or AM251 did not alter the activity of the tested G proteins even at considerably high ligand concentrations.