

# Differential coupling of the human cannabinoid receptors hCB<sub>1</sub>R and hCB<sub>2</sub>R to the G-protein G<sub>α<sub>i2</sub>β<sub>1</sub>γ<sub>2</sub></sub>

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## Abstract

Human cannabinoid receptors 1 (hCB<sub>1</sub>R) and 2 (hCB<sub>2</sub>R) are expressed in the CNS and couple to G<sub>i</sub>/G<sub>o</sub>-proteins. The aim of this study was to compare coupling of hCB<sub>1</sub>R and hCB<sub>2</sub>R to G<sub>α<sub>i2</sub>β<sub>1</sub>γ<sub>2</sub></sub> in Sf9 insect cells. High-affinity agonist binding at hCB<sub>1</sub>R, but not at hCB<sub>2</sub>R, was resistant to guanine nucleotides. hCB<sub>1</sub>R activated G<sub>α<sub>i2</sub>β<sub>1</sub>γ<sub>2</sub></sub> much more rapidly than hCB<sub>2</sub>R in the [<sup>35</sup>S]guanosine 5'-[γ-thio]triphosphate ([<sup>35</sup>S]GTP<sub>γ</sub>S) binding assay. Moreover, hCB<sub>1</sub>R exhibited a higher constitutive activity than hCB<sub>2</sub>R as assessed by the relative inhibitory effects of inverse agonists on [<sup>35</sup>S]GTP<sub>γ</sub>S binding and steady-state high-affinity GTPase activity compared to the stimulatory effects of the hCB<sub>1/2</sub>R agonist CP 55,940 [(-)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol]. G<sub>α<sub>i2</sub>β<sub>1</sub>γ<sub>2</sub></sub> coupled to hCB<sub>2</sub>R exhibited higher GDP- and GTP<sub>γ</sub>S-affinities than G<sub>α<sub>i2</sub>β<sub>1</sub>γ<sub>2</sub></sub> coupled to hCB<sub>1</sub>R. NaCl effectively reduced constitutive activity of hCB<sub>1</sub>R but not of hCB<sub>2</sub>R. Collectively, hCB<sub>1</sub>R and hCB<sub>2</sub>R couple differentially to G<sub>α<sub>i2</sub>β<sub>1</sub>γ<sub>2</sub></sub>. Moreover, hCB<sub>1</sub>R exhibits higher constitutive activity than hCB<sub>2</sub>R. These differences point to distinct functions of hCB<sub>1</sub>R and hCB<sub>2</sub>R in the CNS.