Cannabidiol is a negative allosteric modulator of the cannabinoid CB_1 receptor

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Abstract

Background and Purpose

Cannabidiol has been reported to act as an antagonist at cannabinoid CB_1 receptors. We hypothesized that cannabidiol would inhibit cannabinoid agonist activity through negative allosteric modulation of CB_1 receptors.

Experimental Approach

Internalization of CB_1 receptors, arrestin2 recruitment, and PLCβ3 and ERK1/2 phosphorylation, were quantified in HEK 293A cells heterologously expressing CB_1 receptors and in the ST*Hdh*$^{Q7/Q7}$ cell model of striatal neurons endogenously expressing CB_1 receptors. Cells were treated with 2-arachidonylglycerol or Δ^9-tetrahydrocannabinol alone and in combination with different concentrations of cannabidiol.

Key Results

Cannabidiol reduced the efficacy and potency of 2-arachidonylglycerol and Δ^9-tetrahydrocannabinol on PLCβ3- and ERK1/2-dependent signalling in cells heterologously (HEK 293A) or endogenously (ST*Hdh*$^{Q7/Q7}$) expressing CB_1 receptors. By reducing arrestin2 recruitment to CB_1 receptors, cannabidiol treatment prevented internalization of these receptors. The allosteric activity of cannabidiol depended upon polar residues being present at positions 98 and 107 in the extracellular amino terminus of the CB_1 receptor.

Conclusions and Implications

Cannabidiol behaved as a non-competitive negative allosteric modulator of CB_1 receptors. Allosteric modulation, in conjunction with effects not mediated by CB_1 receptors, may explain the *in vivo* effects of cannabidiol. Allosteric modulators of CB_1 receptors have the potential to treat CNS and peripheral disorders while avoiding the adverse effects associated with orthosteric agonism or antagonism of these receptors.