Cannabigerol Modulates the Efficacy of Anandamide On the CB2 Cannabinoid Receptor

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Abstract

Cannabigerol (CBG) is a non-psychoactive phytocannabinoid isolated from cannabis. The aim of this study was to measure the modulation of CBG on the effects of several synthetic and endocannabinoid agonists on the human CB2 cannabinoid receptor stably expressed in HEK293 cells. A homogeneous time-resolved fluorescence method was used to quantify cannabinoid-induced, CB2-mediated inhibition of cyclic adenosine monophosphate (cAMP) levels. At concentrations up to 10 µM, CBG by itself had no effect on forskolin-stimulated cAMP accumulation. Furthermore, CBG did not significantly modify cAMP inhibition induced by synthetic cannabinoids CP-55,940, HU-210, or endocannabinoid 2-arachidonoylglycerol (2-AG). However, CBG was found to increase the efficacy of endocannabinoid anandamide (AEA). Taken together, these results demonstrate that CBG is neither an orthosteric agonist nor an antagonist at the CB2 receptor. In addition, these data suggest that CBG possibly changes the efficacy of AEA on CB2 receptor via metabolic modulation.

Background

Very little has been published regarding CBG's binding capabilities to the cannabinoid receptors. Even less has been published regarding agonism or antagonism of the receptors by CBG. It has been shown that CBG binds with low affinity to both the CB1 and CB2 receptors, with slightly higher affinity for CB1 [1,2,3]. One group has shown that CBG antagonizes the CB1 receptor, but states that further study is needed for CB2 receptor agonism/antagonism [1].

Specific Aims

1. Determine if CBG is an agonist/ antagonist for the CB2 receptor, and determine if CBG modulates the effect of other cannabinoid agonists on CB2 using an HTRF cAMP assay.
2. Determine if CBG binds orthosterically to the CB2 receptor using a competition binding assay.
3. Determine if CBG binds allosterically to the CB2 receptor using a dissociation kinetic assay.
4. Determine if CBG modulates anandamide degradation using thin layer chromatography (TLC).

Results

Figure 1: Effect of CBG on Forskolin- stimulated cAMP accumulation

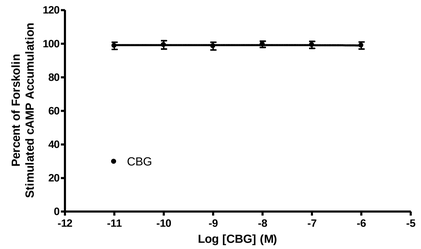
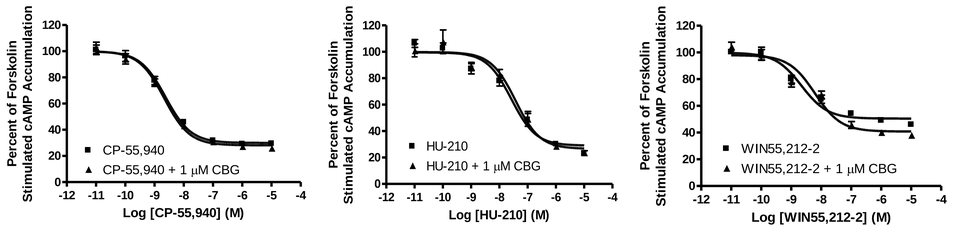


Figure 2: Effect of CBG on forskolin- stimulated cAMP accumulation by known cannabinoid agonists



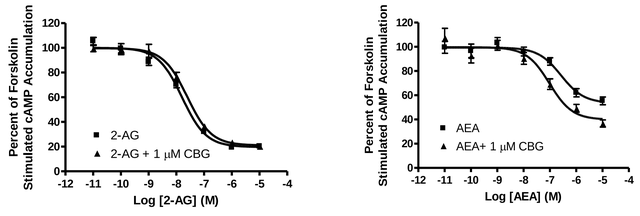


Figure 3: Competition of [3H]WIN55,212-2 binding by CBG

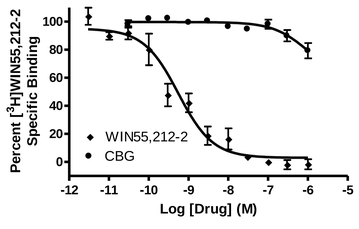


Figure 4: Effect of CBG on [3H]WIN55,212-2 dissociation from the CB2 receptor

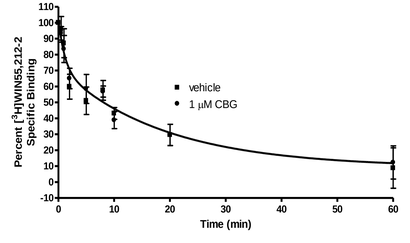
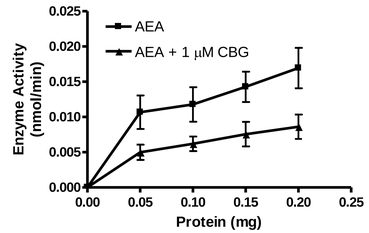


Figure 5: Effect of CBG on Anandamide degradation



Conclusions

1. CBG is not an agonist or antagonist for the CB2 receptor, but potentiates the effect of anandamide on CB2.
2. CBG binds to the orthosteric site of CB2 with low affinity, and does not bind allosterically.
3. CBG reduces AEA degradation, which may explain increase in efficacy observed in the cAMP assay.

References

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