THE PHYTOCANNABINOID, CANNABIDIOL BEHAVES AS A CB₂ RECEPTOR INVERSE AGONIST.

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We have reported previously that the non-psychotropic phytocannabinoid, cannabidiol (CBD), opposes the ability of cannabinoid receptor agonists to inhibit electrically-evoked contractions of the mouse isolated vas deferens with a potency greater than expected from its affinity for CB₁ or CB₂ receptors (Pertwee et al., 2002). We have also found that, by itself, CBD can enhance the amplitude of electrically-evoked contractions of this tissue. The present investigation was directed at exploring the ability of CBD to behave as an antagonist/inverse agonist at human CB₂ receptors.

All experiments were performed with CHO cells transfected with human CB₂ receptors (CB₂-CHO cells). The [³⁵S]GTPγS binding assay was used to determine both the efficacy of CBD and the ability of CBD to antagonize the cannabinoid agonist CP55940 at the CB₂ receptor. Displacement of [³H]CP55940 was used to measure the affinity of CBD for the CB₂ receptor. These results were then compared with those obtained with the established CB₂ receptor antagonist/inverse agonist SR144528. Details of the assays conditions used are described in Thomas et al. (2005). Values are expressed as means, and variability as 95% confidence intervals, shown in brackets. The Kᵢ values were calculated using the equation of Cheng and Prusoff (1973), one-sample t-tests were performed to establish whether cannabinoi ds significantly changed the level of [³⁵S]GTPγS binding, and Schild analysis was used to determine the apparent Kᵢ values. A P-value <0.05 was considered significant.

At a concentration of 1 µM, CBD was found to antagonize CP55940 with an apparent Kᵢ of 65.1 nM (15.6 and 227.9 nM) that was 64.5 times less than its CB₂ Kᵢ value of 4.2 µM (2.9 and 6.2 µM). The corresponding apparent Kᵢ of SR144528, 0.49 nM (0.26 and 0.85 nM), was also found to be significantly less (x 15) than its CB₂ Kᵢ value, which was 7.5 nM (5.8 and 9.8 nM). In addition to producing a rightward shift of the CP55940 log concentration-response curves both CBD and SR144528 produced a significant downward displacement. It was then discovered that by themselves, CBD and SR144528 each inhibited [³⁵S]GTPγS binding to CB₂-CHO cell membranes. Although the inhibitory efficacy of CBD matched that of SR144528, CBD was about 1000 times less potent. When we re-analysed our data, in a manner expected to exclude the inhibitory effect that these cannabinoids produced by themselves, we found that the antagonism by SR144528 was reduced and that by CBD was abolished altogether.

In contrast to SR144528, CBD may be the first example of a ligand that can produce an inverse effect at the CB₂ receptor at a concentration below that which causes little or no displacement of [³H]CP55940 from this receptor. CBD may prove useful as an anti-inflammatory agent since there is evidence that CB₂ receptor inverse agonism can inhibit immune cell migration (Lunn et al., 2006).


Funded by GW Pharmaceuticals.