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Br J Pharmacol. 2014 Sep 26. doi: 10.1111/bph.12944. [Epub ahead of print]

Are cannabidiol and Δ9 -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review.

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Abstract

Based on evidence that the therapeutic properties of Cannabis preparations are not solely dependent on the presence of Δ^9 -tetrahydrocannabinol (THC), pharmacological studies have been recently carried out with other plant cannabinoids (phytocannabinoids), particularly cannabidiol (CBD) and Δ^9 -tetrahydrocannabivarin (THCV). Results from some of these studies have fostered the view that CBD and THCV modulate the effects of THC via direct blockade of cannabinoid type-1 (CB_1) receptors, thus behaving like first generation CB_1 inverse agonists, such as rimonabant. Here we review in vitro and ex vivo mechanistic studies of CBD and THCV, and synthesize data from these studies in a meta-analysis. Synthesized data regarding mechanisms are then used to interpret results from recent preclinical animal studies and clinical trials. The evidence indicates that CBD and THCV are not rimonabant-like in their action, and thus appear very unlikely to produce unwanted central nervous system effects. They exhibit markedly disparate pharmacological profiles particularly at CB_1 receptors: CBD is a very low affinity CB_1 ligand which can nevertheless affect CB_1 activity in vivo in an indirect manner, whilst THCV is a high affinity CB_1 ligand and potent antagonist in vitro and yet only occasionally produces effects in vivo resulting from CB_1 antagonism. THCV also has high affinity for CB_2 and signals as a partial agonist, a departure from both CBD and rimonabant. These cannabinoids illustrate how in vitro mechanistic studies do not always predict in vivo pharmacology, and underlie the necessity of testing compounds in vivo before drawing any conclusion on their functional activity at a given target.

PMID:25257544[PubMed - as supplied by publisher]

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