The 11-hydroxy Metabolite Of Δ^9-Tetrahydrocannabivarin Behaves As An Apparent CB_1 and CB_2 Receptor *Neutral* Antagonist

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We have reported previously that the phytocannabinoid, Δ^9-tetrahydrocannabivarin (Δ^9-THCV), can behave as a CB_1 receptor antagonist (Pertwee et al., 2007), and as a CB_2 receptor partial agonist (Bolognini et al., 2010). We now report results from experiments directed at investigating the ability of the Δ^9-THCV metabolite, 11-OH-Δ^9-THCV, to target cannabinoid CB_1 and CB_2 receptors.

In our investigation, we performed both [^{3}H]CP55940 displacement binding assays with membranes obtained from MF1 mouse whole brain, hCB_1 and hCB_2 CHO cells, and [^{35}S]GTPγS binding assays, performed with these membranes or with MF1 mouse spleen membranes, using methods we have described previously (Cascio et al., 2010; Bolognini et al., 2010). Mean apparent K_B values for 11-OH-Δ^9-THCV (1 μM) were calculated by Schild analysis.

Table: K_i (nM), maximum displacement (%), E_{max} (%) and K_B (nM) values, with 95% confidence limits (CL), for 11-OH-Δ^9-THCV determined using mouse brain, mouse spleen, human CB_1 CHO cell or human CB_2 CHO cell membranes

Tissue	K_i (nM) 95% CL	Displ. (%) 95% CL	n	E_{max} (%) 95% CL	n	K_B (nM) 95% CL	n
Brain	22.4 12.9 & 39.0	89.7 84.3 & 95.2	6	-	6	127.8 44.0 & 370.7	8
hCB_1	27.6 13.6 & 55.9	94.7 86.2 & 103.2	6	-36.2 -43.9 & -28.5	8	ND	
hCB_2	119.1 92.4 & 153.5	93.6 89.5 & 97.7	6	-	8	89.4 18.6 & 430.4	8
Spleen	-	-		-		304.0 42.1 & 2197	5-7

When tested alone, 11-OH-Δ^9-THCV (1nM-10μM) did not affect [^{35}S]GTPγS binding to either mouse brain or hCB_2 CHO cell membranes. Also, at 1 μM, 11-OH-Δ^9-THCV induced a rightward, but not a downward, shift of the log concentration-response curve of CP55940 in mouse brain membranes, hCB_2 CHO cell and mouse spleen membranes, thus behaving as an

apparent CB_1 and CB_2 "neutral" antagonist. K_B values are reported in the Table above. Consequently, 11-OH-Δ^9-THCV may be an important lead compound for a much needed *neutral* CB_2 receptor antagonist. It will be important, therefore, to establish whether, like Δ^9-THCV (Bolognini et al., 2010), 11-OH-Δ^9-THCV behaves as a CB_2 partial agonist when the measured response is CB_2-mediated inhibition of cyclic AMP production.

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Pertwee RG et al, Br J Pharmacol 150:586, 2007

Bolognini D et al, Br J Pharmacol 160:677, 2010

Cascio MG et al, Br J Pharmacol 159:129, 2010