THE PHYTOCANNABINOID Δ9-TETRAHYDROCANNABIVARIN MODULATES SYNAPTIC TRANSMISSION AT CENTRAL INHIBITORY SYNAPSES

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The cannabinoid receptors CB_1 and CB_2 are G protein-coupled receptors, predominantly linked via $G_{i/o}$ subunits to the inhibition of adenylate cyclase. In addition to being the molecular targets for endocannabinoids, cannabinoid receptors can also be activated by phytocannabinoids present in *Cannabis sativa*. In the cerebellum, an important centre for movement and balance, CB_1 receptors localised to basket cell interneurone (IN) terminals onto Purkinje cells (PCs) modulate inhibitory GABAergic transmission (Diana *et al*., 2002). The phytocannabinoid, Δ9-tetrahydrocannabivarin (THCV) has been recently shown to have functional effects in the periphery (Thomas *et al*., 2005); in the current study, the effects of THCV were examined at IN-PC synapses and actions compared with synthetic receptor agents to reveal the first reports of functional central effects for THCV.

Whole cell voltage-clamp recordings of miniature inhibitory postsynaptic currents (mIPSCs) were made from PCs in parasagittal cerebellar slices prepared from 3-5 week old male TO mice (10-20 g) in accordance with Home Office-approved procedures. The CB_1/CB_2 agonist, WIN55,212-2 (5 μM), the selective CB_1 antagonist, AM251 (2 μM) or THCV (5.8 μM) were bath applied in the presence of TTX, NBQX and CGP 55845. Drugs were made as 1000 x stock solutions in vehicle (DMSO (WIN55,212-2 AM251 and CGP 55845); ethanol (THCV) or water (TTX, NBQX)) and dissolved to final concentrations in standard aCSF. Changes in mean mIPSC amplitude and frequency were analysed at steady-state; holding potential was -70mV and experiments performed at RT.

WIN55,212-2 caused a reduction in mean mIPSC frequency of 37.7 ± 2.1 % (n=25, paired *t*-test $P<0.001$). The WIN55,212-2-induced reduction was reversed by AM251; in 8 cells tested, mIPSC frequency typically was increased above control levels (138 ± 9.6 %, n=8; ANOVA plus Tukey's HSD test $P<0.01$). In addition, AM251 applied alone caused a further significant increase in mIPSC frequency from control values (143 ± 8.7 %, n=6; paired t-test $P<0.001$). The WIN55,212-2-induced reduction was also reversed by THCV; in 6 cells tested, mIPSC frequency typically was increased above control levels (158 ± 15 %, n=6; ANOVA plus Tukey's HSD test $P<0.05$). In addition, THCV applied alone caused a further significant increase in mIPSC frequency from control values (199 ± 32 %, n=6; paired t-test $P<0.001$). In all cases, mean mIPSC amplitude was not significantly changed throughout experiments, consistent with a presynaptic site of action.

These data are consistent with THCV acting at cannabinoid receptors at central IN-PC synapses. Overall, the increase in GABA release caused by THCV or AM251 suggests either an antagonism of basal inhibition (e.g. caused by endocannabinoid release) or an inverse agonist effect at CB_1 receptors in this preparation.

Diana MA *et al*. (2002). *J Neurosci* **22**: 200-208.
Thomas A *et al.* (2005). *Br J Pharmacol* **146**: 917-926.

Work supported by The Wellcome Trust. THCV was a kind gift from GW Pharmaceuticals.