TETRAHYDROCANNABIVARIN EXHIBITS ANTICONVULSANT EFFECTS IN A PIRIFORM CORTICAL BRAIN SLICE MODEL OF EPILEPTIFORM ACTIVITY

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Cannabis has been historically used as an anticonvulsant by epilepsy sufferers as long ago as the 1840s (O'Shaughnessy, 1842), although more recent research has highlighted both pro- (Kalant, 2004) and anti-convulsant (Alger, 2004) effects of cannabinoids, suggesting that pro-/anti-seizure activity may be dependent upon the relative phytocannabinoid content within herbal cannabis preparations (Whalley *et al.*, 2004).

The potential pro-/anti-convulsant activity of one such phytocannabinoid, Δ^9-tetrahydrocannabivarin (THCV) (Thomas *et al.*, 2005), was investigated using a Mg^{2+}-free model of epileptiform activity in acute transverse rat (P>40; female; Hampshire (outbred)) piriform cortical (PC) brain slices (Whalley *et al.*, 2005; 2006) and recorded electrophysiologically at room temperature with an extracellular multi-electrode array system (8x8 electrode array). Spontaneous bursts were induced using Mg^{2+}-free Krebs medium (15 min exposure) and bath-applied THCV (5 μM in ethanol; final bath ethanol concentration ≤0.001%, 15 min; n=5 for all data; significance by paired t-test; data shown as mean ± s.e.m.) reduced the frequency of bursts (control: 0.03 ± 0.001 Hz; THCV: 0.01 ± 0.001 Hz; P<0.05), and peak-to-peak burst amplitude (control: 124 ± 21 μV; THCV: 68 ± 17 μV; P<0.05). In addition, THCV reduced both the early negative (N) (control: 201 ± 32 μV; THCV: 85 ± 19 μV; P<0.05) and late positive (P) (control: 126 ± 32 μV; THCV: 17 ± 11 μV; P<0.05) wave components of the epileptiform field potential evoked following intrinsic (PC layer II/III) fibre stimulation (4V monopolar) and recorded at the burst focus. Moreover, spontaneous bursting was found to spread from a single recording focus (0.71 μm^2) across the whole of the recorded area (2.66 mm^2) in control slices, but was limited to an area of 0.27 ± 0.02 mm^2 around the focus in the presence of THCV, suggesting an inhibition of seizure propagation. Interestingly, in control medium, THCV (5 μM) had no obvious effect upon the evoked early non-NMDA-mediated P-wave (control: 82 ± 21 μV; THCV: 91 ± 18 μV; P>0.5) and only slightly suppressed the late P wave (control: 107 ± 17 μV; THCV: 68 ± 18 μV; P<0.1).

These results suggest that THCV had little effect on normal activity in the piriform cortex whilst clearly disrupting the spread of epileptiform activity and thus may act as a novel anticonvulsant component within herbal cannabis.

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