Acute Δ^9-tetrahydrocannabinol-induced alterations in ZIF268 MRNA expression in a murine feeding paradigm

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For some 20 years, cannabinoids (CBs) have been approved in the clinic to treat the appetite loss and body weight reduction seen in wasting syndromes. Recently the appetite stimulating properties of CBs have been robustly demonstrated in rat (Williams *et al.*, 1998) and, to a lesser extent, in mouse models (Wiley *et al.*, 2005). The question as to how CBs modulate food intake remains to be fully elucidated. A number of hypothalamic areas have been implicated, including the paraventricular and ventromedial nuclei, as well as extrahypothalamic nuclei such as the nucleus accumbens and the hippocampus (Harrold *et al.*, 2002; Jamshidi and Taylor, 2001; Verty *et al.*, 2005). We have found no studies examining the brain areas activated during a CB-induced feeding response. In addition, few studies have been undertaken in mice. We therefore sought to map brain nuclei activation after acute Δ^9-tetrahydrocannabinol (Δ^9-THC) administration in a murine feeding paradigm.

Male C57/BL6J mice (18-26g) were fasted for 18 hours prior to the beginning of the dark period, when they were injected with vehicle, 0.01, 0.5 or 3 mg/kg Δ^9-THC IP (n = 12). Thirty minutes after injections pre-weighed palatable pellets were placed in the test chamber and food intake, feeding behaviour (frequency and duration) and locomotor activity (LMA) were simultaneously monitored for 45 minutes. Mice were then euthanized, the brains frozen and sectioned (20 μm) at 8 coronal levels. A ^{33}P labelled *zif268* probe was hybridised to the brain sections and the resultant autoradiograms were quantified for relative optical density (ROD) bilaterally at 39 loci. Food intake, feeding behaviours and LMA were all analysed using a one-way ANOVA. The ROD of each brain region was analysed by a two-way ANOVA (with dose as a between subjects factor and laterality as a within subjects factor) followed by a *post hoc* Dunnett t-test.

No significant differences in food intake were detected between vehicle and Δ^9-THC (0.01, 0.5 or 3.0 mg kg^{-1}) treated groups (0.75 ± 0.08g, 0.86 ± 0.05g, 0.77 ± 0.07g, 0.73 ± 0.07g respectively; $p = 0.536$). However, 3mg kg^{-1} Δ^9-THC treated mice spent a longer duration eating compared with control (32 ± 4% vs 22 ± 2%; $p < 0.05$). At this dose, there were also changes in *zif268* expression in 6 brain regions: reductions in visual ($p < 0.01$), somatosensory ($p < 0.05$), cingulate ($p < 0.05$) and ventral orbital ($p < 0.01$) cortices and increases in posterior ($p < 0.05$) and ventromedial ($p < 0.01$) hypothalamic areas. Interactions between treatment and laterality was also observed in a further 5 brain regions, including the nucleus accumbens and the ventral tegmental area.

This is the first demonstration of dissociation between effects on neural activation in hypothalamic and extrahypothalamic areas following acute Δ^9-THC administration.

Harrold *et al.* (2002) *Brain Res* **952**: 232-238
Jamshidi *et al.* (2001) *Br J Pharmacol* **134**: 1151-1154
Verty *et al.* (2005) *Neuropharmacology* **49**: 1101-1109
Wiley *et al.* (2005) *Br J Pharmacol* **145**: 293-300
Williams *et al.* (1998) *Physiol Behav* **65**: 343-346