BOLD response to the agonist THC and to the selective antagonist, Rimonabant: an fMRI study in the rat brain

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INTRODUCTION

THC (Δ^9-tetrahydrocannabinol) increases feeding in sated rats by acting on central reward systems. Therefore it has been suggested that cannabinoid receptor 1 antagonists or inverse agonists could be used to treat obesity, as has lead to the CB1 cannabinoid receptor antagonist Sanofi-Aventis compound, rimonabant, to be tested in phase 3 clinical trials.[1] We used pharmacological challenge fMRI (pMRI) to compare brain Blood Oxygen Level Dependent (BOLD) signals produced by 1 mg/kg THC with those elicited by rimonabant[2] (1 mg/kg) that produces a reduction in food intake.

METHODS

Rats were imaged in a 7T magnet for 70 minutes under alpha-chloralose anaesthesia, and injected intraperitoneally with 1 mg/kg THC (n=10) or its vehicle (n=10); 1 mg/kg rimonabant (n=8) or its vehicle (n=7). A T_2*-weighted gradient echo sequence was used to record brain volumes every 70s (TR = 172ms, TE = 15ms, matrix 128 x 64, 4 averages). Twelve brain volumes were acquired prior to injection, and imaging was continued for a further 48 volumes. Brain volumes were realigned and normalised to an in-house template using SPM2 and a first level analysis performed by comparing post drug/vehicle infusion time bins (12 min of data) to the pre-infusion period. SPM2 was then used in a second level analysis to determine brain areas with significant changes in BOLD contrast following treatment compared with the appropriate controls.

RESULTS

Overall, THC and rimonabant had strikingly opposite effects. Rimonabant increased BOLD signal in sensory and motor, as well as in limbic regions of the brain: orbitofrontal cortex, sensory, association and motor nuclei of the thalamus, caudate putamen, pallidum, substantia nigra, rubral fields and cerebellum, core of the nucleus accumbens, hippocampus, bed nucleus of the stria terminalis, lateral septum, preoptic area, brainstem reticular nuclei and nucleus tractus solitarius. THC produced either decreased or no signal in these areas. THC increased BOLD signal in olfactory cortical areas and the anterior amygdala, but had no effect in the hypothalamus, areas that displayed decreased signal with rimonabant.

DISCUSSION AND CONCLUSION

It is difficult at this stage to attribute regional brain activity to specific effects of the drugs. However, these results suggest that rimonabant may reduce food intake by acting on the limbic forebrain. This is supported by the fact that the receptor agonist, THC, had weak though consistently opposite effects in these areas. In addition, changes in BOLD signal were observed in motor systems. This is consistent with the known actions of cannabinoids, though no altered motor behaviour following this dose of rimonabant is reported in the literature.

REFERENCES

1. Van Gaal *et al*., 2005, Lancet 365: 1389
2. Tucci et al., 2004, Br J Pharmacol. 143(5): 520

Rimonabant was a gift from Sanofi-Aventis.