The cannabinoid CB1 receptor antagonist SR141716A attenuates the memory impairment produced by Delta 9-tetrahydrocannabinol but not the changes in bdnf levels

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Delta 9-tetrahydrocannabinol (THC) is the primary psychoactive compound of *Cannabis sativa*, one of the oldest drugs of abuse. Learning and memory acquisition involves short-term changes in both electrical properties and long-term synaptic structural alterations (Dalley *et al.*, 2004). Neuronal survival, maintenance and growth depends on target-derived trophic factors, such as brain-derived neurotrophic factor (BDNF). It has been proposed that BDNF significantly modulates these synaptic changes and that its expression is upregulated during memory acquisition (Kanhema *et al.,* 2006). In the present study the effects of chronic THC and the CB1 antagonist SR141716A on novel object discrimination, and levels of BDNF and TrkB receptor-like immunoreactivities in the hippocampus and prefrontal cortex were investigated.

Male Lister hooded rats (n=32 250-300g; Charles River UK), all experiments were performed under UK Home Office regulations (Project license 40/2715) and carried out at the University of Nottingham. THC (2 mg/kg, Sigma UK) or SR141716A (2 mg/kg) or SR141716A+THC (30 mins between treatment) were administered every 48 hours for 21 days and controls were given vehicle (Cremophor/ethanol/saline 1:1:18). Object recognition was carried out as previously described (Ennaceur *et al.,* 2005) and protein levels were measured using Western blots (antibodies: anti-BDNF, Santa Cruz Biotechnology; anti-TrkB, Upstate Biotechnology). Data were analysed by Student's paired t-test and one-way ANOVA.

Using an object recognition paradigm, vehicle treated rats discriminated between the familiar and novel objects ($p<0.05$) while THC treated rats were unable to discriminate between the objects during the choice trial ($p>0.05$) indicating that THC impaired working memory with a one hour retention interval between the sample and choice trials. SR141716A on its own significantly enhanced working memory ($p<0.001$), and pre-treatment with SR141716A reversed the THC-induced memory impairment ($p<0.01$). BDNF levels in the hippocampus and prefrontal cortex were significantly increased in THC and SR141716A+THC treated rats compared to control rats ($p<0.05$ and $p<0.01$ respectively) with no effect of SR141716A on its own. Pre-treatment with the CB1 antagonist SR141716A on THC-treated rats failed to reverse the changes in the BDNF levels. In the hippocampus, TrkB receptor protein levels were significantly reduced ($p<0.05$) in THC treated rats, an effect not seen in rats given SR141716A and THC.

These findings indicate that chronic THC impairs working memory, and increases hippocampal and prefrontal cortex levels of BDNF. The effects on working memory, but not BDNF levels, were reversed by pre-treatment with SR141716A. Therefore, we conclude that the cognitive deficit appears to be CB1 receptor mediated but effects of THC on BDNF may be regulated through a different non CB1 receptor mediated mechanism.

Dalley et al. 2004. Neurosci Biobehav Rev. **28**(7):771-84
Ennaceur et al. 2005. Behav Brain Res. **159**(2):247-66
Kanhema et al. 2006. J Neurochem. **99**(5):1328-37