

NIAA Final Report: Nuffield Fund

Dr Nadia Ladak MBChB FRCA MPhil

Royal College of Anaesthetist small research grant for “The Role of cannabinoids in Sepsis” project, awarded October 2010. This grant part funded a larger body of work for which I was awarded a Masters of Philosophy degree, by the University of Leicester.

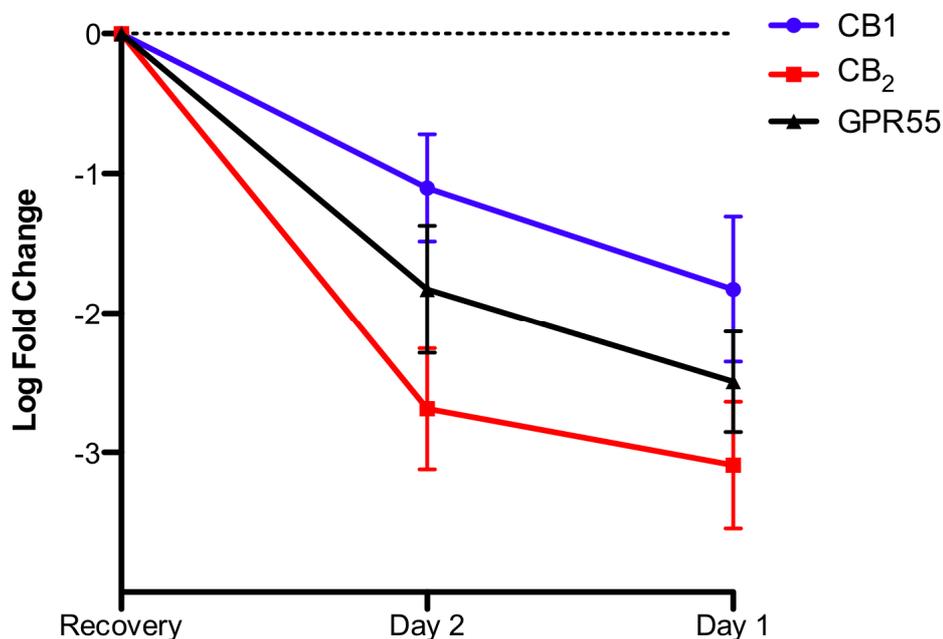
Introduction

There is growing evidence for an involvement of the cannabinoid system in the pathogenesis of sepsis. *In-vitro*, immune cell activation increases endocannabinoid release and reduces metabolic breakdown. The net result of this increased endocannabinoid activity may contribute to some of the cardiovascular changes seen in sepsis, as shown in previous studies. (1,2)

Methods

Following ethics approval we have recruited 49 intensive care patients with a diagnosis of sepsis, and followed up 26 patients into the recovery period. The mRNA expression of cannabinoid receptors and enzymes on polymorphonuclear cells were quantified by polymerase chain reaction (PCR).

Results



Our PCR study showed downregulation of the 3 cannabinoid receptor mRNA in septic patients compared to the matching recovery samples (Mean values and SEM are plotted in above graph).

In this study we also showed that human polymorphonuclear cells express mRNA for the second FAAH enzyme FAAH-2. There is reduced mRNA expression of both FAAH enzymes in patients diagnosed with sepsis compared to their matched recovery sample.

This was the first report of both the GPR55 receptor and FAAH2 enzyme mRNA present in polymorphonuclear cells.

Conclusions

Down-regulation of the endocannabinoid enzymes leads to an accumulation of endocannabinoids, which is thought to be a factor in hypotension associated with sepsis.

Our previous in-vitro studies (3) have shown up-regulation of the cannabinoid receptors. *In-vitro* conditions can never replicate the complex conditions of *in-vivo* sepsis; the complex cellular interactions and feedback, also the timing of the initial septic insult is difficult to determine and septic patients requiring ICU admission may have an exacerbated response to a septic insult.

References

1. Cannabinoids and Sepsis. **Ladak N**, Beishon L, Thompson J.P., Lambert D.G. *Trends in Anaesthesia and Critical care* 2011; **1**: 191-198
2. Plasma endocannabinoid concentrations in sepsis. **Ladak N**, Lam P.M.W, Serrano Gomez A, McDonald J, Konje J.C, Thompson J. P, Lambert D. G. *British Journal of Anaesthesia* 2010; 105:719P(Abstract)
3. Lipopolysaccharide treatment upregulates CB2 cannabinoid receptors on human neutrophils. **Ladak N**, Young S. P, McDonald J, Thompson J. P, Lambert D. G. *British Journal of Anaesthesia* 2009; 103: 322-323 (Abstract)