

## EFFECTS OF FATTY ACID AMIDE HYDROLASE AND CYCLOOXYGENASE-2 INHIBITORS ON NOCICEPTIVE BEHAVIOUR IN THE CARRAGEENAN MODEL OF INFLAMMATORY PAIN IN RATS

Ian Robinson, Denise Richardson, Maulik Javeri, David A. Barrett, David A Kendall and Victoria Chapman. School of Biomedical Sciences and Institute of Neuroscience, University of Nottingham, NG72UH, UK.

Cannabinoids and endocannabinoids (ECs) produce well described anti-nociceptive effects via the activation of cannabinoid CB<sub>1</sub> receptors, which are present on primary afferent fibres as well as spinal and supraspinal neurones. The ECs are primarily metabolised by fatty acid amide hydrolase (FAAH) but are also substrates for inducible cyclooxygenase (COX2) (Kozak *et al.*, 2002). Systemic administration of the FAAH inhibitor (URB597, (3'-(aminocarbonyl)[1,1'-biphenyl]-3-yl)-cyclohexylcarbamate) has been shown to attenuate hyperalgesia associated with the carrageenan model of inflammatory pain (Holt *et al.*, 2005). The aim of the present study was to compare the effects of local hindpaw injection of the FAAH inhibitor URB597 with a COX2 inhibitor (nimesulide) that has no effect on FAAH activity, on nociceptive behaviour in the carrageenan model of inflammatory pain.

Weight bearing on the left and right hindpaw was measured with an Incapacitance tester (Linton Instrumentation, U.K.), in male Sprague-Dawley rats, weighing 240-260g. Rats received an intraplantar injection of nimesulide (50µg in 50µl), URB597 (25 or 100 µg in 50µl) or vehicle (50µl 3% Tween 80 in saline), 30 minutes prior to intraplantar injection of 2% carrageenan or saline (100µl). Weight bearing on the left (injected) and right hindpaw was assessed 10 minutes prior to injection of carrageenan/saline and at 90, 150 and 210 minutes post-injection. Weight bearing data were analysed using a two-way ANOVA with a Bonferroni correction for multiple comparisons.

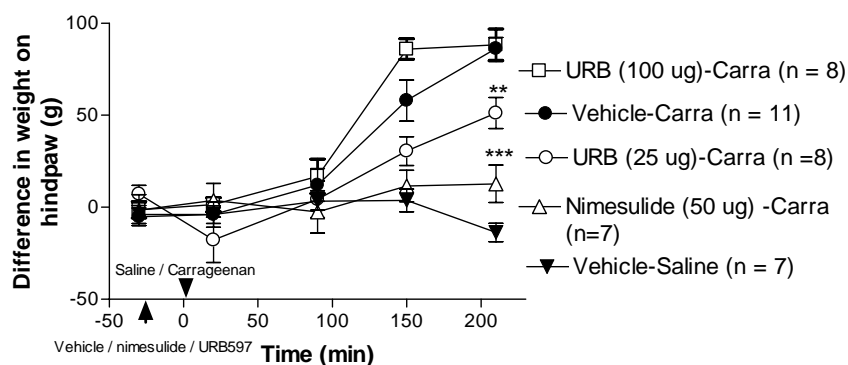


Fig.1 Effects of intraplantar injection of URB597 and nimesulide on carrageenan-induced changes in weight bearing behaviour. Data are expressed as means  $\pm$  SEM of differences in weight bearing between contralateral and ipsilateral hindpaws. \*\*  $p < 0.01$  \*\*\*  $p < 0.001$  compared to Vehicle-Carra .

Intraplantar injection of carrageenan significantly enhanced the difference in weight bearing between ipsilateral and contralateral hindpaws compared to saline injection ( $p < 0.001$ ). Intraplantar injection of URB597 (25µg) or nimesulide (50µg) significantly reduced the difference in weight bearing compared to the vehicle-carrageenan group (Figure 1). In contrast, the higher dose of URB597 did not significantly alter the carrageenan induced changes in weight bearing. Although the lack of effect of the higher dose of URB597 requires further investigation, these data demonstrate that local peripheral inhibition of FAAH and COX2 can reduce nociceptive behaviour in the carrageenan model of inflammatory pain.

Holt *et al.*, (2005) *Br J Pharmacol*, **146**, 467-76.

Kozak *et al.*, (2002) *J Biol Chem*, **277**, 44877-85