THE FAAH INHIBITOR URB597 REVERSES INFLAMMATORY PAIN THROUGH A CB1 RECEPTOR MEDIATED MECHANISM

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Fatty acid amide hydrolase (FAAH) is a membrane bound enzyme responsible for the catalysis of the endocannabinoid, anandamide. FAAH knockout mice have been shown to have elevated levels of anandamide in several brain regions (Clement et. al., 2003) and also to display CB1 mediated analgesia (Cravatt et. al., 2001). More recently, FAAH inhibitors have also been shown to produce analgesic effects in rodents (Kathuria et. al., 2003). In the present study we have examined the effects of the FAAH inhibitor, URB597 [3' carbamoyl-biphenyl-3-yl-cyclohexylcarbamate] in models of established inflammatory pain. In subsequent studies the effect of the CB1 and CB2 receptor antagonists, AM281 (0.5mg/kg, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-4-morpholinyl-1H-pyrazole-3-carboxamide) and AM630 (15mg/kg, (6-Iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl)(4-methoxy-phenyl methanone), on the response to URB597 was investigated in the FCA model. Male Random Hooded rats (180-240g) were used in all studies. Freund's Complete Adjuvant (FCA, 50 or 100µl of 1mg/ml) was injected subcutaneously into the plantar surface of the hind paw. 23hrs later URB597 was dosed (0.1-3mg/kg s.c.) and the FCA-induced decrease in weight bearing on the inflamed left hind paw (WB; Clayton et al., 1997) or paw withdrawal threshold (PP; Randall & Selitto, 1957) was determined 1 hr later. The antagonist studies were performed as for the WB FCA study above, with the antagonists being administered i.p. 30 minutes prior to URB597 (2mg/kg, s.c.). Data are mean±s.e.mean. Where appropriate, geometric mean and 95% confidence intervals for ED_{50} values were calculated. ANOVA followed by Duncan's post-hoc comparisons determined whether there was a significant difference (* $p<0.05$) between vehicle and drug treated groups. URB597 produced a significant and dose dependent reversal of established FCA induced hyperalgesia following both WB ($p<0.05$) and PP ($p<0.05$) assessment (Table 1.), with ED_{50} values of 0.86mg/kg (0.44-1.66) and 0.36mg/kg (0.04-3.28), respectively. Administration of the CB1 receptor antagonist AM281 significantly ($p<0.05$) reversed the URB597 mediated inhibition of hypersensitivity using a WB assessment, whereas the CB2 receptor antagonist, AM630, did not ($p>0.05$, Table 2). These data demonstrate the potential analgesic properties of FAAH inhibition in inflammatory pain, and further delineate a role for the CB1 receptor in this mechanism.

Table 1.

Treatment	% Reversal	
	WB	PP
Vehicle	0	16.0±5.3
0.1	28.3±8.3	31.4±6.9*
0.3	-	43.8±3.1*
1	45.6±6.4*	-
2	71.0±10.4*	-
3	-	83.6±12.7*

Table 2.

Treatment	WB difference (g)
Vehicle	93.7±12.1
URB597	13.6±9.2*
AM281	101.0±9.5
AM630	82.7±11.6
URB597&AM281	84.7±11.2
URB597&AM630	16.9±8.9*

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