ANTI-HYPERSENSITIVE AND ANTI-INFLAMATORY ACTIVITY OF THE POTENT AND SELECTIVE CB2 AGONIST GW842166X

N.M.Clayton,_A.W.Wilson, S.D.Collins, G.M. Giblin, B.L. Mitchell, P. Goldsmith, I.P. Chessell, C. O'Shaughnessy, C, Bountra. Neurology & GI CEDD, GlaxoSmithkline, New Frontiers Science Park, Harlow, Essex, CM19 5AW.

We have previously shown that the selective CB2 agonist L-768,242 inhibited carrageenan -induced inflammation and hypersensitivity to pain (Clayton et al., 2002). The aim of this study was to investigate the effect of the novel, potent and highly selective CB2 agonist GW842166X (2-(2, 4-Dichlorophenylamino)-4-trifluoromethylpyrimidine-5-carboxylic acid [(tetrahydropyran-4-yl)methyl]amide; CB2 EC_{50} =55nM (human), 50nM (rat), CB1 EC_{50} >100µM (human), >10µM (rat)) in models of chronic inflammatory and neuropathic hypersensitivity to pain. Male Random Hooded rats (180-240g) were used in all studies.

In established FCA, 100µl of 1mg/ml Freund's Complete adjuvant (FCA) was injected intraplantar into the left hind paw and 23hrs later GW842166X (0.03-10mg/kg) was dosed orally. One hr post dose the effect of GW842166X on FCA-induced decrease in weight bearing on the inflamed left hind paw (dual channel weight averager: Clayton et al., 1997) and increase in paw volume (plethysmometer) was determined. In a model of chronic inflammatory joint pain, 150µl of FCA was injected into the left knee joint (intra-articular injection) under gaseous anaesthetic and then allowed to recover. On day 13 when the hypersensitivity (weight bearing) and joint diameter (hand held digital micrometer) was stable, GW842166X (5-15mg/kg, b.i.d. p.o.) was dosed for 5 days and the effect on the FCA induced decrease in weight bearing and increase in joint diameter was determined 1hr after the morning dose on each day. In a model of neuropathic pain (chronic constriction injury, CCI) the sciatic nerve in the left leg was loosely ligated with 4 ligatures of chromic 4.0 gut. On day 22 post surgery, when the hypersensitivity (paw pressure, Randall & Selitto, 1957) was maximal and stable, GW842166X (15mg/kg b.i.d., p.o.) was dosed for 8 days. The effect on the CCI induced decrease in paw pressure was determined as above. Data is presented as mean±s.e. mean. Where appropriate geometric mean and 95% confidence intervals for ED_{50} values were calculated. Statistical analysis was carried out to determine whether there was a significant difference *(*$p<0.05$) between the vehicle and drug treated group using Student's unpaired *t* test (eFCA) or Anova followed by Duncan' post-hoc comparisons (chronic joint pain). In the FCA model GW842166X produced a dose related reversal of the hypersensitivity (max reversal: 98±10%@0.3mg/kg., $p<0.05$, ED_{50}=0.07(0.03-0.2)mg/kg) and reduced the paw oedema (max reversal: 25±5%@0.3mg/kg, $p<0.05$). In chronic joint pain, GW842166X produced a significant reversal of the FCA induced decrease in weight bearing on the ipsilateral limb (max reversal: 50%@15mg/kg) and reduced the joint diameter ($p<0.05$). The effect was maximal by day 5 of dosing. In CCI, chronic dosing of GW842166X produced a significant reversal of the CCI induced decrease in paw withdrawal threshold (max reversal: 58% on day 8, $p<0.05$). #

In conclusion, the CB2 agonist GW842166X fully reversed established inflammatory hypersensitivity, reduced chronic joint hypersensitivity and reduced the paw oedema and joint diameter respectively. In a model of neuropathic hypersensitivity to pain GW842166X significantly reduced the hypersensitivity to pain. The data suggests that GW842166X may have clinical utility in both chronic inflammatory and neuropathic pain.

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