70-P47 A novel COX-2 inhibitor GW406381X attenuates spontaneous ectopic discharge of sural nerve in rats with chronic constriction injury (CCI).

Zhao, F-Y[1]., Spanswick, D[1]., Martindale, J. C.[2], Reeve, A.J.[2], Chessell, I. P.[2] [1]NeuroSolutions Ltd, PO Box 3517, Coventry CV4 7ZS, UK and [2]Neurology & GI CEDD, Glaxo Smith Kline Pharmaceuticals, 3rd Avenue, Harlow, Essex, CM19 5AD, UK

Introduction

The efficacy of COX-2 inhibitors in treating chronic inflammatory diseases such as rheumatoid arthritis is well established. However, the evidence on efficacy of COX-2 inhibitors in treating neuropathic pain remains controversial.

In this study, we have investigated the effect of chronic dosing with GW406381X, a novel COX-2 inhibitor, on paw withdrawal thresholds (PWTs) and spontaneous ectopic discharge of sural nerve filaments in CCI rats.

Methods

Neuropathic pain model:

Chronic constriction injury (CCI) was created on male adult Sprague-Dawley rats by placing 4 loose ligations on the left sciatic nerve. The neuropathic pain state was assessed by measuring paw withdrawal thresholds using von Frey hairs and a paw pressure Analgesy-meter.

Drug administration:

From 14 days post surgery, the rats were orally dosed either with GW406381X 5mg/kg, rofecoxib 5mg/kg or the same volume of vehicle, twice daily for 5 days.

Electrophysiological Recording:

After the treatments, the PWTs were re-assessed and the rats were anaesthetized with sodium pentobarbitione for recording ectopic discharge of sural nerve fibres.

Results

1. GW406381X significantly reversed the lowered PWTs observed in CCI rats, compared to the vehicle control.
2. Rofecoxib had no significant effect on the PWTs (Figures 1 and 2).
3. In GW406381X-treated rats, but not in rofecoxib-treated rats, the proportion of fibres displaying spontaneous ectopic discharge and the frequency of spontaneous ectopic discharge were significantly lower than those in vehicle control rats. (Figures 3, 4 and 5)

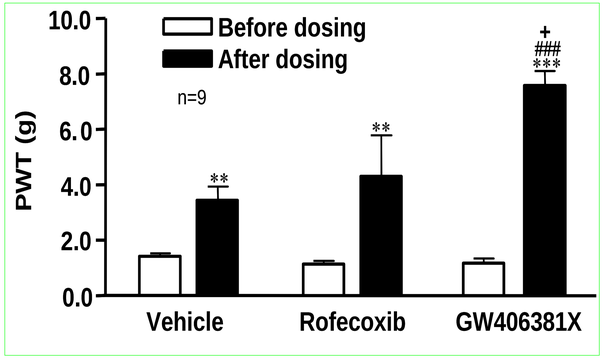


Figure 1. Effect of vehicle, rofecoxib and GW406381X on the Paw Withdrawal Threshold (PWT) in response to von Frey hair stimulation in ipsilateral (CCI) side before and after drug application. **, ***: compared to the value before drug dosing, *P*<0.01, 0.001. ###: compared to vehicle group after drug administration, *P*<0.001; +: compared to rofecoxib group after 5-day drug administration, *P*<0.01.

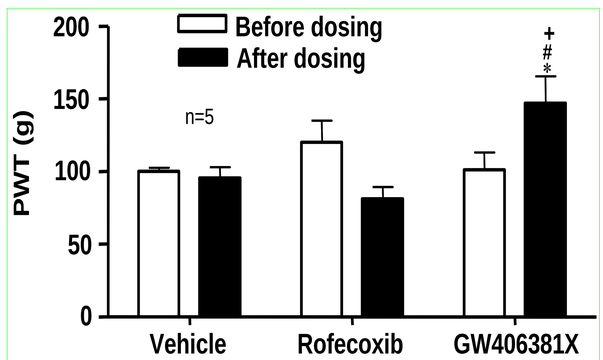


Figure 2. Changes of Paw Withdrawal Threshold in response to paw pressure (Randall-Selitto test) after 5-day oral vehicle or drug administration in ipsilateral (CCI) side. Before vehicle or drug dosing, there is no significant difference in PWT among the vehicle, rofecoxib and GW406381X groups. After 5-day dosing, in vehicle or rofecoxib treated groups PWT was not significantly changed, *P*>0.05. In GW406381X treated rats, however, the PWT was significantly increased after dosing, compared to pre-dosing, P<0.05 and was significantly higher compared to that recorded from vehicle and rofecoxib treated rats (*P*<0.05, # and +).

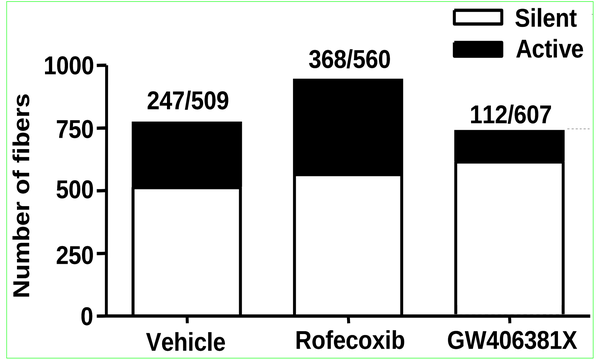


Figure 3. Percentage (proportion) of fibres with spontaneous activity in all fibres examined in vehicle-, rofecoxib- and GW406381X treated CCI rats (n=8 in each group). The number over each column represents the numbers of 'active' and 'silent' units from different groups. The percentage of active fibres is significantly lower in GW406381X treated rats, *P*<0.001 compared to the vehicle and rofecoxib treated rats.

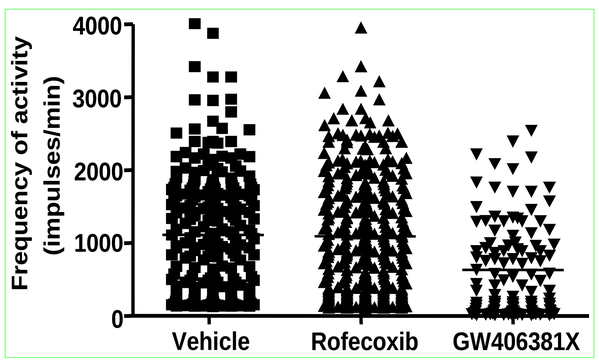


Figure 4. Frequencies of spontaneous activity in active fibres recorded from vehicle-, rofecoxib- and GW406381X treated CCI rats.

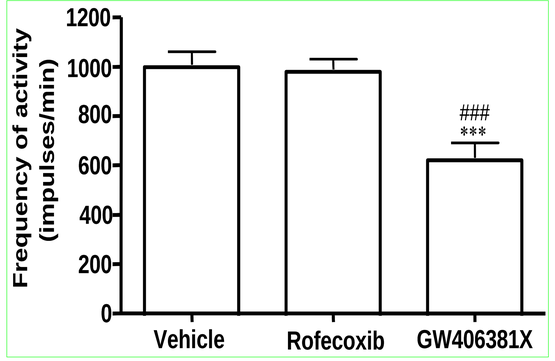


Figure 5. Averaged frequencies of activity in vehicle, rofecoxib and GW406381X treated CCI rats (8 rats in each group, 247, 368 and 112 units in vehicle, rofecoxib and GW406381X groups, respectively, see also figure 4.). ***: compared to the vehicle group, P<0.001; ###: compared to rofecoxib group, P<0.001.

Conclusions

1. GW406381X is effective in reversing the hypersensitivity observed in the CCI model of neuropathic pain rats.
2. GW406381 also reduced the proportion of fibres displaying ectopic discharge and frequency of this discharge in anaesthetized rats.
3. COX-2 may play an important role in the maintenance of neuropathic pain following nerve injury.
4. The therapeutic effect of COX-2 inhibitors may depend on the particular structure of compounds and the dynamic interaction of drug and enzyme.

NEUROSolutions LTD.

NEUROLOGY & GI CEDD

gsk GlaxoSmithKline