Genomic Effects Of GW0742, a Peroxisome Proliferator Activated Receptor (PPAR) β/δ Agonist On Rat Bronchi

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Peroxisome Proliferator activated receptors (PPARs) are therapeutic targets in the treatment of inflammatory lung disease. We have recently shown that the PPARβ/δ agonist GW0742 relaxes pulmonary, aorta and mesenteric arteries in mice, and has therapeutic benefits in pulmonary hypertension in rats (Harrington et al., 2010). Despite evidence of ubiquitous PPARβ/δ expression relatively little is known about its effects in the airways.

Male Sprague Dawley rats (200-250g) were killed by cervical dislocation, and the bronchi mounted into isometric wire myographs. Bronchi were contracted with EC_{50} concentrations of acetylcholine (Ach) and responses to increasing concentrations of GW0742 (10^{-6} to 10^{-4} M) measured. Some bronchi were incubated overnight with GW0742 (3x10^{-5} M) and/or the protein synthesis inhibitor cyclohexamide (CHX; 1.4x10^{-5} M), before contractions to Ach measured. Rat bronchi did not relax in response to GW0742 given acutely at concentrations up to 10^{-4} M, where 33.4 ± 5.1% relaxation was seen compared to -10.4 ± 2.8% in time controls (n=4). Overnight incubation (chronic exposure) of airway tissue with 3x10^{-5} M GW0742 reduced broncho-constriction in response to Ach (Figure 1) an effect that was prevented by co-incubation with CHX (Figure 1).

![Figure 1](image_url)

Figure 1. Data shown is mean ± SEM, n=3; * p<0.05 by two way ANOVA compared to control or GW0742 plus CHX.

These findings suggest that activation of PPARβ/δ and subsequent gene induction/ new protein synthesis protects the airways from bronchospasm and may have therapeutic indications in inflammatory lung diseases.

Harrington et al., 2010 PloS ONE 5(3) e9526