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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_{80} concentrations of acetylcholine (Ach) and responses to increasing concentrations of GW0742 (10^{-6} to 10^{-4}M) measured. Some bronchi were incubated for 16 hours with GW0742 ($3x10^{-5}$M) and/or the protein synthesis inhibitor cyclohexamide (CHX; $1.4x10^{-5}$M) at 37.5°C, 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% SEM relaxation was seen compared to -10.4 ± 2.8% SEM in time controls (n=4). Overnight incubation (chronic exposure) of airway tissue with $3x10^{-5}$M GW0742 reduced broncho-contraction in response to Ach (Figure 1) an effect that was prevented by co-incubation with CHX (Figure 1).

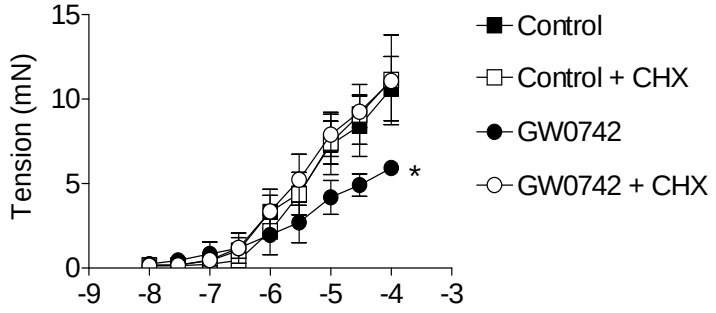

Figure 1. Effect of 16hr incubation with GW0742 +/- Cyclohexamide on Acetylcholine induced broncho-contraction. *Data shown is mean ± SEM, n=3; * p<0.05 by two way ANOVA compared to control or GW0742 plus CHX.*

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.