PPART-DEPENDENT AND -INDEPENDENT INHIBITION OF HUMAN CULTURED AIRWAY SMOOTH MUSCLE PROLIFERATION AND CYTOKINE RELEASE BY ROSIGLITAZONE

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Peroxisome proliferator activated receptor γ (PPARγ) is a ligand-activated transcription factor that regulates indices of proliferation & inflammation in airway smooth muscle (ASM). Therefore, there is therapeutic potential for PPARγ ligands such as rosiglitazone (RG) to regulate airway wall remodelling & inflammation in asthma. The PPARγ dependence of the modulation of ASM function by RG was examined using the PPARγ-specific, irreversible antagonist, GW 9662 (GW). In ASM from lung transplant recipients, thrombin- (0.3 U/mL) or bFGF- (300 pm) mediated proliferation was assessed by cell enumeration. Supernatant levels of granulocyte macrophage-colony stimulating factor (GM-CSF) & PGE2 in the presence of IL-1α (1 ng/mL) were measured by ELISA & RIA, respectively. The PPARγ antagonist, GW, reversed inhibition of thrombin-mediated proliferation by RG (% unstimulated cell number, thrombin 132 ± 2%, + RG (10 µM) 98 ± 6%, + RG + GW (1 µM) 127 ± 3%, n = 6, P < 0.05 cf thrombin).

However, there was no reversal of the inhibition of bFGF-mediated proliferation (bFGF 146 ± 5%, + RG 102 ± 7%, + RG + GW 110 ± 5%, n = 6). GW did not reverse inhibition of IL-1α-stimulated GM-CSF levels by RG (% IL-1α-stimulated response, IL-1α + RG 54 ± 2%, IL-1α + RG + GW 63 ± 3%, n = 6). Rosiglitazone increased IL-1α-stimulated PGE2 levels, but GW was unable to prevent this increase (IL-1α + RG 259 ± 56%, IL-1α + RG + GW 265 ± 66%, n = 6). These data support the conclusion that the PPARγ dependence of the effects of rosiglitazone may be stimulus-dependent.

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