Selective Prostacyclin Receptor Agonism Augments Glucocorticoid-induced Gene Expression in Human Bronchial Epithelial Cells

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Prostacyclin receptor (IP) agonists display anti-inflammatory and anti-viral activity in cell-based assays and in pre-clinical models of asthma and chronic obstructive pulmonary disease. We have extended these observations by demonstrating that IP-receptor activation also can enhance the ability of glucocorticoids to induce genes with anti-inflammatory activity. BEAS-2B bronchial epithelial cells stably transfected with a glucocorticoid response element (GRE) luciferase reporter were activated in a concentration-dependent manner by the glucocorticoid, dexamethasone \( (p[A]_{50} = 7.96 \pm 0.11; E_{\text{max}} = 19.3 \pm 3.8\text{-fold}) \). An IP-receptor agonist, taprostene, increased cAMP in these cells \( (p[A]_{50} = 8.01 \pm 0.01) \) and augmented luciferase expression at all concentrations of dexamethasone examined. Analysis of the concentration-response relationship that described this effect showed that taprostene increased the magnitude of transcription (~ 2-fold) without affecting the potency of dexamethasone \( (p[A]_{50} = 7.73 \pm 0.2) \) and was, thus, steroid-sparing in this simple system. RO3244794, an IP-receptor antagonist, and oligonucleotides that selectively silenced the IP-receptor gene, PTGIR, abolished these effects of taprostene. Infection of BEAS-2B GRE reporter cells with an adenovirus vector (Ad5.CMV.PKI\( \alpha \)) encoding a highly selective inhibitor of cAMP-dependent protein kinase (PKA) also prevented taprostene from enhancing GRE-dependent transcription. In BEAS-2B cells and primary cultures of human airway epithelial cells, taprostene and dexamethasone interacted in either an additive or positive cooperative manner in the expression of three glucocorticoid-inducible genes (glucocorticoid-induced leucine zipper [GILZ], mitogen-activated protein kinase phosphatase-1 [MKP-1] and kinase inhibitor protein 2 of 57 kDa [p57\( ^{kip2} \)]) that have anti-inflammatory potential. Collectively, these data show that IP-receptor agonists can augment the ability of glucocorticoids to induce anti-inflammatory genes in human airway epithelial cells by activating a cAMP/PKA-dependent mechanism. This observation may have clinical relevance in the treatment of airway inflammatory diseases that are either refractory, or respond sub-optimally, to glucocorticoids.