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Title: Inhibition of phosphodiesterase 4B enhances glucocorticoid-dependent gene transcription in human airway epithelial cells: Implications for the treatment of COPD

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Body: Clinical trials involving severe COPD patients showed that PDE4 inhibitor, roflumilast (ROF) reduced exacerbations in patients taking inhaled corticosteroids (ICS) concomitantly. We hypothesised that this clinical benefit is due, in part, to the ability of ROF to augment the ability of glucocorticoids to induce anti-inflammatory genes. Using a glucocorticoid response element (GRE) luciferase reporter stably transfected into human airway epithelial cells, fluticasone propionate (FP) induced GRE-dependent transcription in a concentration-dependent manner. However, concurrent addition of ROF with FP enhanced transcription above that produced by FP alone. Similarly, silencing PDE4B, one of the four PDE4 isogenes, also augmented FP-induced transcription above that produced by FP alone whereas silencing PDE4A, PDE4C & PDE4D was ineffective. Selective PDE4B inhibitor augmented FP-induced transcription in a concentration-dependent manner where a selective PDE4D inhibitor had no effect. We have shown that the β2-adrenoceptor agonist, formoterol, enhanced GRE-dependent transcription. In presence of low concentrations of PDE4B inhibitor, formoterol concentration-response curve was displaced to the left indicating that cells had become more sensitive to β2-adrenoceptor agonist-induced-GRE-dependent transcription whereas the PDE4D inhibitor was inactive. Our data support the tenet that an ICS and PDE4 inhibitor in combination imparts clinical benefit in COPD beyond that provided by an ICS alone. Our data also suggest that inhibition of PDE4B is a primary target that mediates the anti-inflammatory effect of PDE4 inhibitors like ROF.