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Title: Aclidinium bromide reduces extracellular matrix deposition by COPD-derived mesenchymal cells

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Body: Background: Addition of muscarinic receptor inhibitors to COPD therapy showed beneficial effects on lung function. Objective: To evaluate the effect of aclidinium bromide and formoterol on deposition and de novo synthesis of extracellular matrix components by human airway smooth muscle cells and fibroblasts. Methods: Primary cells from patients with stage III COPD (n=7) and non-COPD controls (n=7) were characterised for α-smooth muscle actin (muscle) and fibronectin (fibroblast) 24 and 48 hours after TGF-β1 stimulation. Deposition and mRNA levels for collagen type-I, III, IV and fibronectin were analysed by ELISA and real-time PCR. Results: TGF-β1 stimulated matrix deposition was significantly reduced by pre-treatment with the drugs for collagen type-I and -III as was fibronectin; but not for collagen type-IV. The reduced collagen and fibronectin deposition correlated with decreased mRNA levels. The reduction of collagen type-III was only observed at the protein level without reduced mRNA synthesis. TGF-β1 stimulated collagen type-I deposition was dose-dependently reduced by aclidinium bromide (10^{-11}-10^{-8} M; max. 32%) and formoterol (10^{-8}-10^{-10}M; max. 18%). When combined, the effect of the drugs was additive. The inhibitory effect of the drugs was similar in fibroblasts and smooth muscle cells. This effect was observed in cells from diseased and non-diseased subjects. Conclusion: The results suggest that aclidinium bromide and formoterol reduce remodelling in the two main mesenchymal cell types of the lung through gene inhibition. Clinical implication: This observation may contribute to the clinically observed improvement of lung function by reducing extracellular matrix deposition.