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Title: Tiotropium and olodaterol exert anti-proliferative effects on pulmonary fibroblasts of asthmatic patients in vitro

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Body: Background: The airway wall remodeling observed in asthma patients involves many cell types, including pulmonary fibroblasts. Although the platelet-derived growth factor (PDGF) and the adreno-cholinergic receptor signaling systems have been implicated in the remodeling process, their interaction is not well defined. Objective: Here, we investigated the role of tiotropium and olodaterol in PDGF-BB-stimulated human lung fibroblast proliferation in vitro. Methods: Fibroblasts were isolated from asthmatic (n=7) and non-asthmatic (n=7) lung tissue biopsies. Cells were stimulated with either: PDGF-BB (10ng/ml), PDGF-BB + tiotropium (10⁻⁷M, 10⁻⁶M), PDGF-BB + olodaterol (10⁻⁷M, 10⁻⁶M), or the combination of PDGF-BB + olodaterol + tiotropium (both drugs at: 10⁻⁷ and 10⁻⁶M) for 3 and 5 days. Tiotropium was always added 30 minutes prior to other factors. Results: PDGF-BB significantly increased the proliferation of fibroblasts of both asthmatic and non-asthmatic origin. at 3 and 5 days; the effect being more pronounced in cells of asthma patient. Both tiotropium (10⁻⁷M, 10⁻⁶ M) and olodaterol (10⁻⁷M, 10⁻⁶M) significantly reduced PDGF-BB-induced proliferation of asthmatic fibroblasts only (p<0.05 for all concentrations at 5 days). In combination, the drugs did not further reduce PDGF-BB-induced fibroproliferation. Conclusion: Our data show that olodaterol and tiotropium, as well as their combination, exert significant anti-proliferative effect in vitro.