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Title: Tiotropium enhances the inhibitory effect of the long acting β2-agonist olodaterol on the release of IL-6 and IL8 by primary human lung fibroblasts of asthma patients

Mr. Luigi 9514 Costa luigi.costa@unibas.ch [1], Prof. Dr Michael 9515 Roth RothMic@uhbs.ch [1], Prof. Dr Michael 9516 Tamm mtamm@uhbs.ch MD [1] and Dr. Pieter 9517 Borger pieter.borger@unibas.ch [1]. [1] Pulmonary Cell Research, Dept of Biomedicine, University Hospital, Basel, Switzerland, 4031 .

Body: Muscarinic and β2-adrenergic receptors of resident lung cells are modulators of airway inflammation and remodeling. Here, we used human primary lung fibroblasts of healthy and asthmatic subjects to investigate the role of β2-adrenergic and muscarinic receptors on the interleukin IL-1β-induced secretion of IL-6 and IL-8. Fibroblasts were isolated from asthmatic (n=5) and non-asthmatic subjects (n=5) and stimulated with IL-1β in the presence or absence of olodaterol (10-6M), tiotropium (10-6M), or with the combination of olodaterol (10-6M) and tiotropium (10-6M). IL-6 and IL-8 levels in the supernatant were measured by ELISA. Neither olodaterol nor tiotropium alone affected the secretion of IL-6 and IL-8 in unstimulated cells. Tiotropium reduced the IL-1β-induced secretion of IL-6 and IL-8 in both control and asthmatic cells ($p<0.05$). Olodaterol reduced IL-1β-induced cytokines in control (IL-6: 52±1%, $n<0.05$; IL-8: 54±16%, $p<0.05$) and asthmatic (IL-6: 76±5%, $n<0.05$; IL-8: 72±2%, $p<0.05$) fibroblasts. Compared to olodaterol alone the combination of olodaterol (10-6M) with tiotropium (10-6M) further reduced the release of IL-6 (55±7%; $p<0.05$) and IL-8 (50±6%; $p<0.05$) from fibroblasts of asthma patients only. Both olodaterol and tiotropium exert anti-inflammatory responses in healthy and asthmatic fibroblasts. The combination of olodaterol with tiotropium further improved the anti-inflammatory effect, specifically in asthmatic fibroblasts. These data provide support for combination therapy of long acting β2-agonists plus long acting muscarinic receptor antagonists. Supported by Boehringer-Ingelheim, Biberach, Germany.