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TIOTROPIUM INCREASES PPARgamma AND DECREASES CREB IN CELLS ISOLATED FROM INDUCED SPUTUM OF COPD PATIENTS

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Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation, chronic inflammation of the airways and lung parenchyma. In pharmacological management of COPD important therapeutic benefits are usually provided by bronchodilators used in polytherapy. Long-acting beta2-agonists (LABA) combined with long-acting antimuscarinic agents (LAMA) such as tiotropium bromide are currently used for the treatment of COPD. Our aim was to assess two elements of intracellular signaling involved in regulation of inflammation in COPD in patients subjected to LABA or LABA+LAMA therapy: expression of peroxisome proliferator-activated receptor gamma (PPARgamma) protein, which has antiinflammatory and immunomodulatory properties and cAMP response element binding protein (CREB) and activated (CREB-P) protein which has histone acetyltransferase activity and mediate increased histone acetylation and transcriptional activation of chromatin. Twenty one stable COPD patients (18 males and 3 females, mean age 65yrs) receiving 12 ug BID Formoterol therapy were assayed before and after three month add-on therapy consisting of and 18 ug QID Tiotropium. In all patients spirometry, lung volumes, and DLCO were performed before and after therapy. All patients were subjected to the sputum induction before and after therapy, sputum cells were isolated and processed to obtain cytosolic and nuclear fractions. PPARgamma, CREB or CREB-P proteins were quantified in WB using specific antibodies against human proteins (Santa Cruz Biotechnology) and enhanced luminescence detection. Mean expression of PPARgamma in cell nuclei was significantly increased (increase by about 180%, $P<0,01$) after therapy while CREB and phosphorylated CREB levels in cytosol and nuclei were decreased (decrease by about 30%, $P<0.05$). Tiotropium add-on therapy improved FEV1 and lung volumes (mean data before and after therapy were: FEV1 - 1,52L, 51,85% vs. 1,73L, 56,3%; IC - 1,87L, 62,4% vs. 2,14L, 71,3%; RV-3,39L, 152% vs. 2,92L, 131,57% and RV/TLC- 52,7 to 47,14%, respectively). Our data show that the mechanism whereby tiotropium reduces exacerbations is not only associated to a persistent increase in airway functions and reduced hyperinflation mediated by muscarinic receptors but also to possible anti-inflammatory effects of the drug involving increased PPARgamma and decreased CREB signaling.