RESTORED HDAC-2 EXPRESSION AFTER CORTICOSTEROID AND THEOPHYLLINE THERAPY IN EX-SMOKER COPD PATIENTS

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Corticosteroids (ICS), which effectively switch off pro-inflammatory genes in asthma are ineffective in Chronic Obstructive Pulmonary Disease (COPD). We assessed the effect of ICS with or without Theophylline on pro-inflammatory signalling pathways in COPD. Thirty seven patients with stable disease received one of three different courses of therapy: Formoterol alone (F), Formoterol/Budesonide (F/ICS), and Formoterol/ICS/Theophylline (F/ICS/Th) b.i.d. for 4 weeks. Lung function was measured before and after treatment. Cytosol, nuclear extracts and acid extracted histones of cells isolated from induced sputum were evaluated for the expression of HDAC-2, acetylated histones ac-H3, and ac-H4, CREB and activated (phosphorylated) CREB (CREB-P), before and after treatment. Results: In Current Smoker patients F/ICS increased HDAC-2 expression 2 fold, up to Ex-Smoker baseline therapy level with no effect of F/ICS/Th. F/ICS/Th increased HDAC-2 expression 2.77 fold in comparison to F/ICS and 1.42 fold of baseline therapy expression in Ex-Smokers. F/ICS increased expression of ac-H3 by 31% ($p<0.001$), but decreased ac-H4 expression by 22% ($p<0.01$). F/ICS/Th decreased ac-H3 by 53% ($p<001$) in comparison to baseline, and further decreased ($P<001$) expression of ac-H4. Expression of CREB was increased in both cytosolic and nuclear fractions by 40% and 24% respectively ($p<0.001$, $p<0.01$), while CREB-P increased by 50% ($p<0.01$) and 51% ($p<0.01$) in both cellular compartments after F/ICS and F/ICS/Th. These findings suggest that F/ICS/Th therapy may be of value in Ex-Smoker COPD patients since it restores HDAC-2 expression in this group of patients.