CYTOPLASM-NUCLEAR TRAFFICKING OF CREB AND CREB PHOSPHORYLATION AT SER133 DURING COPD THERAPY

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cAMP responsive element binding protein (CREB) plays important role in transcriptional machinery. CREB signaling is clearly altered in patients with asthma and its activity is affected by several drugs including glucocorticoids, theophylline and inhaled β-agonists. However, the role of CREB in chronic obstructive pulmonary disease (COPD), which is related to dysregulation of several pro/antiinflamatory genes is less clear. It is postulated that CREB influences chromatin signaling in COPD, but there is no strong clinical data supporting this statement. We assessed the changes in CREB subcellular distribution (cytosol/nuclei), cytoplasmic and nuclear CREB activation via its phosphorylation at Ser 133 in thirty five stable COPD patients treated with 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 and nuclear extracts isolated from induced sputum leucocytes were evaluated for the expression of CREB and phosphorylated CREB (CREB-P) before and after treatment. Expression of CREB was increased after F/ICS and F/ICS/Th in both cytosolic and nuclear fractions by 40% and 24%, respectively ($P<0.001$, $P<0.01$), while CREB-P increased by 50% and 51% ($P<0.01$) in both cellular compartments after F/ICS and F/ICS/Th. These findings suggest, that activated CREB-related signaling pathways/ proinflammatory genes may result in poor response to ICS therapy.