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Title: Cigarette smoke modulates the PKAc-associated cross-coupling between NF-kB and glucocorticoid receptor in primary small airway epithelial cells

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Body: Negative transcriptional regulation or cross-coupling between NF-kB and glucocorticoid receptor (GR) is proposed to play a regulatory role in human physiology and inflammatory diseases, such as Chronic Obstructive Pulmonary Disease. It has been shown that catalytic subunit of protein kinase A (PKAc) directly phosphorylates GR, activates GR-dependent DNA binding, and also associates with RelA in the cytoplasm promoting its phosphorylation in ser-276. We evaluated the effects of Cigarette Smoke Extract (CSE 10%), on PKAc-associated cross-coupling between NF-kB and glucocorticoid receptor in primary small airway epithelial cells (SAEC11566), using co-immunoprecipitation and Western Blot analysis. We show that PKAc associates with GR in a ligand-independent manner, and with RelA(p65) at baseline. In unstimulated SAEC, Fluticasone Propionate (FP) (0.1μM) increases GR/PKAc association, promoting GR phosphorylation and its nuclear translocation, depending on PKA signaling, since the use of H89 (20mM), a potent inhibitor of PKAc, significantly reduces the FP-induced GR activation. The stimulation of the cells with CSE attenuates, at cytosolic level, FP-induced GR cross-repression of NF-kB, promoting the association of PKAc with RelA(p65)/NF-kB, the p65 phosphorylation on ser-276 and its nuclear translocation. Our results localize the NF-kB and GR cross-coupling to the cytoplasm of SAEC and implicate PKAc-dependent signaling as a potential molecular interface in the negative regulation of anti-inflammatory GR activity in response to oxidative stress induced by cigarette smoke.