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Title: Corticosteroid insensitivity in severe asthma: Impaired nuclear translocation of glucocorticoid receptor in airway smooth muscle cells

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Body: Background: Patients with severe asthma respond poorly to corticosteroids (CS). Airway smooth muscle cells (ASMC) of severe asthma display CS insensitivity. CS mediate their effects through activation of the glucocorticoid receptor (GR) and suppression of NF-κB activity. Aims and objectives: Compare protein/mRNA, phosphorylation, and nuclear translocation of GR and NF-κB (p65). Methods: ASMC of the healthy (9), non-severe (NSA; 8) and severe asthmatics (SA; 8) were obtained from endobronchial biopsies, cultured at passage 4-5. Cells were treated with TNF-α (10 ng/ml)/dexamethasone (Dex; 10^-7 or 10^-6 M). Whole cell protein or nuclear extracts were assessed by Western Blot, mRNA by qRT-PCR. Results: TNF-α induced greater p65 in SA, whereas baseline and TNFα-induced nuclear abundance, and Dex suppression of p65 expression, were similar between groups. GR expressed in asthma was 49% of that in the healthy (p<0.01), with no difference between NSA and SA. Dex-induced nuclear translocation of GR in SA was approximately 60% of that in either the healthy or NSA at 30 min-2h, whereas baseline levels were similar. In healthy subjects, Dex maximally induced GR phosphorylation at S211 at 1 hr (5.2-fold vs baseline; p<0.001), which was maintained over 4 hr; phosphorylation status at 2 hr showed no difference between groups. Conclusions: Baseline GR is decreased in ASMCs of asthma, while induced GR translocation is impaired only in SA. Although TNF-α induces greater p65 expression in SA, nuclear translocation and Dex suppression of p65 expression are similar between all groups. Impaired nuclear translocation may underlie the mechanism of CS insensitivity in SA.