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Title: Lipopolysacharide modulates glucocorticoid receptor function in nasal mucosa and polyp fibroblasts

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Body: BACKGROUND: Glucocorticoids are used in the treatment of viral and bacterial-related chronic airway disease exacerbations, such as asthma and nasal polyposis, although they do not effectively suppress them. Infections may contribute to disease deterioration by inducing glucocorticoid insensitivity/resistance. AIM: To elucidate whether lipopolysaccharide (LPS) reduces glucocorticoid receptor (GR) function in nasal mucosa and nasal polyp fibroblasts. METHODS: Nasal polyp fibroblasts from asthmatic patients (n= 12) and control nasal mucosa fibroblasts (n= 10) were isolated and stimulated in vitro with LPS (10 mg/ml) for 24 h prior to dexamethasone addition for different concentrations and times. Cytokine/chemokine secretion was measured by ELISA and Cytometric Bead Array, the expression of GRα, GRβ, mitogen-activated protein-kinase phosphatase-1 (MKP-1) and glucocorticoid-induced leucine zipper (GILZ) by RT-PCR and immunoblotting, and GRα/β nuclear translocation by immunocytochemistry. RESULTS: LPS increased (P< 0.05) the release of IL-6, IL-8, GM-CSF, RANTES and eotaxin in nasal mucosa and polyp fibroblasts. LPS partially abrogated (P< 0.05) dexamethasone-mediated inhibition of IL-6, IL-8 and GM-CSF. LPS did not alter GRα or GRβ expression or dexamethasone-induced nuclear translocation. LPS increased (P< 0.05) dexamethasone-induced expression of MKP-1 and reduced (P< 0.05) dexamethasone-induced expression of GILZ. CONCLUSION: Repression of GR signalling by bacterial products like LPS may contribute to the low clinical efficacy of glucocorticoids in the treatment of infectious-related inflammatory diseases.