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MECHANISMS AND RESISTANCE IN GLUCOCORTICOID CONTROL OF INFLAMMATION IN PATIENTS WITH ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Glucocorticoids are widely used for the treatment of chronic obstructive pulmonary disease (COPD) and asthma because of their anti-inflammatory properties. However their therapeutic effectiveness is significantly limited in asthma and COPD. Molecular mechanisms of steroid resistance include defective glucocorticoid receptor (GR) binding and translocation into the nucleus, increased expression of GRβ isoform, elevated expression of macrophage migration inhibitory factor (MIF), decreased expression of mitogen-activated protein kinase phosphatase 1 (MKP-1) and histone deacetylase 2 (HDAC2). HDAC2 is involved in suppression of inflammatory genes by glucocorticoids, and its reduced activity and expression are the result of oxidative and nitrative stress induced by cigarette smoke. Oxidative stress causes activation of phosphoinositide-3-kinase δ (PI3Kδ), which leads to phosphorylation (activation) of Akt kinase, phosphorylation (inhibition) of glycogen synthase kinase 3β and phosphorylation (inactivation) of HDAC2. Understanding of the mechanisms leading to steroid resistance allowed to identify drugs targeting this condition. Antidepressant nortriptyline and macrolide solithromycin reverse corticosteroid resistance through inhibition of Akt phosphorylation. Combination of glucocorticoid and long-acting β_2-agonist increases GR nuclear translocation and inhibits Akt phosphorylation. The phosphodiesterase 4 inhibitor roflumilast in combination with dexamethasone improves steroid responsiveness through modulation of PI3Kδ, HDAC2, MKP-1, MIF and GRβ expression. Investigation of the molecular mechanisms of steroid resistance can increase anti-inflammatory properties of steroids and lead to more effective COPD and asthma treatment.