1 Glucocorticoids and Asthma

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1.1 Molecular Mechanisms

Corticosteroids are highly effective anti-inflammatory therapy in asthma, and the molecular mechanisms involved in suppression of allergic inflammation are now better understood (Barnes 1998, 2001). Corticosteroids are effective clinically because they block many of the inflammatory pathways that are abnormally activated in asthma and they have a very broad spectrum of anti-inflammatory actions.

1.1.1 Molecular Basis of Asthma

In asthma there is a persistent inflammation in the airways characterised by infiltration of eosinophils and activation of T-lymphocytes, particular T helper-2 cells and mast cells. There are characteristic structural changes including shedding of airway epithelial cells, fibrosis under the epithelial cells and proliferation of airway smooth muscle cells (Busse

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and Lemanske 2001). This is an increased expression of multiple inflammatory proteins in structural cells of the airways, including cytokines, enzymes that synthesise inflammatory mediators, adhesion molecules and inflammatory receptors. This is largely due to increased gene expression, which has suggested that transcription factors play a critical role in orchestrating the inflammatory process in asthma (Barnes and Adcock 1998). These transcription factors include nuclear factor (NF)-κB and activator protein (AP)-1, both of which are activated in asthmatic airways and result in the expression of many of the inflammatory genes abnormally expressed in the airways of asthmatic patients (Demoly et al. 1992; Hart et al. 1998). In addition, other transcription factors, including nuclear factor of activated T-cells (NF-AT), signal transduction activated transcription factors (STATs) and GATA transcription factors are involved in inflammatory gene expression in asthma (Caramori et al. 1998; Holtzman et al. 1998). Since corticosteroids are very effective in suppressing inflammation in asthmatic airways, it is likely that they are working at the level of inflammatory gene transcription.

1.1.2 Increased Gene Transcription

Corticosteroids produce their effect on responsive cells by activating the glucocorticoid receptor (GR) to directly or indirectly regulate the transcription of certain target genes (Reichardt et al. 1998). In the airways, GR is expressed in all cells, but in a particularly high concentration in airway epithelial and endothelial cells (Adcock et al. 1996). There is no evidence for reduced expression of GR in airways of asthmatic patients, even after treatment with inhaled corticosteroids.

The number of genes per cell directly regulated by corticosteroids is estimated to be between 10 and 100, but many genes are indirectly regulated through an interaction with other transcription factors. GR dimers bind to DNA at consensus sites termed glucocorticoid response elements (GREs) in the 5'-upstream promoter region of steroid-responsive genes. This interaction changes the rate of transcription, resulting in either induction or repression of the gene. Interaction of the activated GR homodimer with GRE usually increases transcription, resulting in increased protein synthesis. GR may increase transcription by interact-