

GLUCOCORTICOIDs are potent inhibitors of inflammatory processes and are widely used in the treatment of asthma. The anti-inflammatory effects are mediated either by direct binding of the glucocorticoid/glucocorticoid receptor complex to glucocorticoid responsive elements in the promoter region of genes, or by an interaction of this complex with other transcription factors, in particular activating protein-1 or nuclear factor- κ B. Glucocorticoids inhibit many inflammation-associated molecules such as cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules. In contrast, anti-inflammatory mediators often are up-regulated by glucocorticoids. *In vivo* studies have shown that treatment of asthmatic patients with inhaled glucocorticoids inhibits the bronchial inflammation and simultaneously improves their lung function. In this review, our current knowledge of the mechanism of action of glucocorticoids and their anti-inflammatory potential in asthma is described. Since bronchial epithelial cells may be important targets for glucocorticoid therapy in asthma, the effects of glucocorticoids on epithelial expressed inflammatory genes will be emphasized.

Key words: Glucocorticoids, Asthma, Bronchial epithelial cells, Inflammation

Glucocorticoids: mechanisms of action and anti-inflammatory potential in asthma

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Introduction

Glucocorticoids are hormones synthesized in the adrenal cortex and secreted into the blood, where the levels of glucocorticoids fluctuate in a circadian mode. In humans, the naturally occurring glucocorticoid is hydrocortisone (cortisol), which is synthesized from its precursor cortisone.

The beneficial effects of glucocorticoids in asthmatic patients were first described in 1950.¹ Since then on, many studies have focused on the therapeutic potential of glucocorticoids. Several synthetic glucocorticoids, much more potent than cortisol and without the unwanted mineralocorticoid side effects, have been developed. Nowadays, glucocorticoids are powerful agents in the treatment of inflammatory diseases and are by far the most effective anti-inflammatory drugs used in the treatment of asthma.

Mechanism of Action

Although glucocorticoids have been known for a long period of time, their precise mechanism of action is still not completely understood. However, recent studies have increased our understanding of their complex mechanisms of action.

Glucocorticoid receptor

To exert their effects, glucocorticoids need to bind to a specific cytoplasmic glucocorticoid receptor (GR). Almost all cells of the body express the GR, but the number of receptors may vary between different cell types.² Cloning of the GR has revealed that the GR consists of approximately 800 amino acid residues, and that certain areas of the molecule show homology with other steroid receptors, receptors for thyroid hormones, and receptors for retinoic acid.^{3–7} All members of the nuclear hormone receptor family share a characteristic three-domain structure, first described for the human GR. The C-terminal domain is equal in size in all nuclear receptors studied (about 250 amino acids) and its main function is to bind the steroid.⁸ It also contains the binding sites for the heat shock proteins (hsp) 90.^{9,10} Removal of the steroid-binding domain results in a constitutively active GR molecule, indicating that this part of the molecule acts as a repressor of the transcription-activation function. The most conserved central domain is involved in direct binding of the receptor to DNA. It contains two distinct loops of protein, each bound at their base via four cysteine residues to a single zinc ion, the so-called zinc fingers.¹¹ These zinc clusters are involved in binding of the GR to the major groove of the DNA double helix and play a role in dimeriza-

tion of two GR molecules.^{12,13} In addition, the central DNA-binding domain has a transcription-activation function.^{4,14} The steroid-binding and DNA-binding domains are separated by the 'hinge-region', which contains sequences that are important for nuclear translocation and dimerization.^{9,10} The N-terminal domain is extremely variable in size (24–600 amino acids). Its precise role is still uncertain, but it is required in transcriptional activation.¹⁵

Two different forms of the human GR have been described.^{3,16} These two highly homologous isoforms, termed GR α and GR β , are generated by alternative splicing of the human GR pre-mRNA. The GR β isoform differs from the GR α isoform only in its C-terminal domain, in which the last 50 amino acids of the latter are replaced by a unique 15 amino acid sequence. However, this replacement has dramatic functional consequences, since the GR β isoform is unable to bind glucocorticoids and to transduce ligand-dependent transactivation. However, the physiological significance of the GR β isoform remains questionable, since some recent studies indicate that this form is not conserved among species and no dominant negative inhibition of GR α activity could be found.^{17,18} Nevertheless, abundant expression of GR β protein can be found in the epithelial cells lining the terminal bronchioli of the lung.¹⁹

The expression of the GR may be regulated by numerous factors either at the transcriptional, translational or post-translational level.^{20,21} Glucocorticoids have been shown to down-regulate the expression of the GR, both *in vitro* and *in vivo*.^{22,23} In contrast, inflammatory mediators like interleukin (IL)-1 β , IL-4, tumour necrosis factor (TNF)- α , lipopolysaccharide (LPS) and interferon (IFN)- γ have been shown to increase glucocorticoid binding *in vitro*.^{24–28} However, the increase in GR numbers may be accompanied by a reduced affinity for glucocorticoids.^{24,28} Analysis of GR localization in normal and asthmatic lung has not revealed differences in the level or sites of GR expression.²⁹

Regulation of gene transcription

In the absence of glucocorticoids, the GR is present in the cytoplasm of the cell as a hetero-oligomer consisting of the GR itself, two molecules of hsp 90, one molecule hsp 70, and one molecule of hsp 56 (which probably does not interact with the GR itself, but interacts with hsp 90).^{30–34} Glucocorticoids enter the cytoplasm of the cell by passive diffusion through the cell membrane. In the cytoplasm they bind to the GR complex, which subsequently undergoes conformational changes, resulting in the dissociation of the hsp 90 and hsp 56 molecules. Upon this activation, the glucocorticoid-GR complex passes the nuclear membrane, enters the nucleus, and the hsp 70 molecule is dissociated.

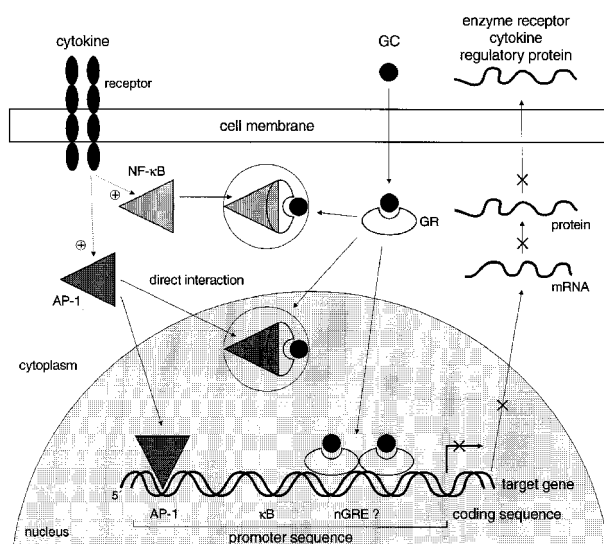


FIG. 1. Schematic representation of the cellular events after administration of glucocorticoids (adapted from Ref. 39).

Furthermore, in the nucleus liganded GR form homodimers (Fig. 1).

Within the nucleus, the GR homodimers may regulate gene transcription in several ways: (1) via binding of the glucocorticoid-GR complex to specific DNA sequences, thereby directly activating or repressing genes; (2) via interaction with other transcription factors; and (3) via modulating the stability of specific mRNA molecules.^{35–39}

Binding to DNA sequences

Several steroid-responsive genes contain glucocorticoid responsive elements (GRE) in their promoter region.^{35,40} Binding of GR homodimers to GRE may either result in transcriptional activation of the gene (via a *positive* GRE) or repression of the gene (via a *negative* GRE) (Fig. 1). The consensus sequence for (positive) GRE is the palindromic 15-base-pair sequence GGTACAnnTGTTCT, whereas the negative GRE has a more variable sequence.³⁶ The rate of transcriptional regulation of steroid-responsive genes is dependent on both the numbers of GRE, the affinity of the glucocorticoid-GR complex to the GRE, and the position of the GRE relative to the transcriptional start site. Binding of the complex to GRE may result in conformational changes in the DNA and exposure of previously masked areas, resulting in increased binding of other transcription factors.^{41–44}

Interaction with other transcription factors

Many steroid-responsive genes do not have GRE in their promoter region. However, binding sites for other transcription factors, including nuclear factor (NF)- κ B, activating protein (AP)-1, and cAMP-responsive element binding protein (CREB), often can be found.⁴⁵

AP-1, which is a dimer of two proto-oncogenes (members of the c-jun and c-fos family),^{46,47} is involved in the regulation of several genes, including adhesion molecules and cytokines (reviewed in Ref. 47). Direct protein-protein interaction between AP-1 and the glucocorticoid-GR complex results in reciprocal repression of one another's transcriptional activation by preventing binding of the AP-1 and glucocorticoid-GR complex to AP-1 sites and GRE, respectively (Fig. 1).^{37,48,49}

Comparable to AP-1, NF- κ B (a heterodimer of p50 and p65 subunits^{50,51}) regulates the transcription of several genes involved in inflammatory reactions.^{50,52,53} In unstimulated cells, NF- κ B is retained in the cytoplasm of the cells through the interaction with the inhibitors I κ B α and I κ B β .⁵⁴⁻⁵⁶ Upon cell stimulation, for example by IL-1 β or TNF- α , I κ B are rapidly phosphorylated, ubiquitinated, and consequently proteolysed.^{53,57} The liberated NF- κ B dimers translocate to the nucleus where they can activate target genes. Glucocorticoids may inhibit NF- κ B-stimulated genes by a direct interaction between the glucocorticoid-GR complex and the p65 subunit of NF- κ B, resulting in transrepression (Fig. 1).^{51,55,58,59} Furthermore, glucocorticoids may indirectly antagonize NF- κ B mediated transcription by up-regulating the synthesis of the inhibitory protein I κ B α , which traps NF- κ B in inactive cytoplasmic complexes.^{39,54,55} A large number of immunoregulatory genes, whose expression is induced by a variety of pro-inflammatory mediators, contain NF- κ B sites in their promoters/regulatory regions. Therefore, it is no wonder that glucocorticoids have been found to prevent the expression of these genes, including those coding for IL-1 β , IL-2, IL-6, IL-8, monocyte chemoattractant protein (MCP)-1, RANTES (Regulated upon Activation, Normal T cell Expressed, and presumably Secreted), granulocyte macrophage colony-stimulating factor (GM-CSF), the IL-2 receptor, intercellular adhesion molecule (ICAM)-1, and E-selectin (reviewed in Ref. 45). Probably, interactions between glucocorticoids and NF- κ B or AP-1 will explain most of the anti-inflammatory and immunosuppressive activities of glucocorticoids.

An interaction between CREB and the glucocorticoid-GR complex has also been suggested.^{60,61} β -agonists, which are used as bronchodilators in the treatment of asthma, increase cAMP formation and subsequently activate CREB. Therefore, simultaneous treatment of asthmatic patients with glucocorticoids and β -agonists may result in reduced responsiveness of the airways for steroids.⁶¹⁻⁶³

Modulation of mRNA stability.

A third mechanism by which glucocorticoids may regulate the synthesis of proteins is via enhanced transcription of specific ribonucleases which are able to degrade mRNA containing constitutive AU-rich sequences in the untranslated 3'-region.⁶⁴ Such gluco-

Table 1. Influence of glucocorticoids on the synthesis of proteins with inflammatory effects by bronchial epithelial cells

Protein	Glucocorticoid effect
Cytokines	
IL-1 β , IL-6, IL-11, TNF- α , GM-CSF	↓
IL-10, LIF	?
G-CSF	=
Chemokines	
MCP-1, eotaxin, IL-8, RANTES, MIP-1 α	↓
Receptors	
NK, GR	✗
IL-1R II, IL-6R, β_2 -adrenergic receptor	✗
Enzymes	
iNOS, COX-2, cPLA ₂	✗
NEP	✗
Adhesion molecules	
ICAM-1	↓
Inhibitory proteins	
Lc-1	↔↑
IL-1RA type I, SPLI	↑

corticoid-mediated modulation of post-translational events (resulting in decreased mRNA stability and reduced half-life time) has been observed for IL-1 β , IL-6 and GM-CSF.^{65,66}

Glucocorticoid Regulated Genes

Glucocorticoids are able to modulate the transcription of a variety of genes, including cytokines and chemokines, receptors, enzymes, adhesion molecules, and inhibitory proteins (Table 1). Since epithelial cells may be one of the most important targets for glucocorticoid therapy in asthma, the effects of glucocorticoids on epithelial expressed inflammatory genes will be emphasized in this review.

Cytokines and chemokines

Glucocorticoids inhibit the transcription of most cytokines and chemokines that are relevant in asthma, including IL-1 β , TNF- α , GM-CSF, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-12, IL-13, RANTES, eotaxin, and macrophage inhibitory protein (MIP)-1 α .^{45,66} In general, reduced synthesis of these mediators may result in a decreased recruitment and activation of leukocytes, also indirectly due to effects on adhesion molecules and cell survival. Since many cytokine gene promoters do not contain a negative GRE, the effects of glucocorticoids on cytokine and chemokine production are probably mediated via an effect on a critical transcription factor (especially NF- κ B and AP-1).⁶⁷ Cross-signalling between NF- κ B and AP-1 with glucocorticoid/GR complex have indeed been demonstrated in bronchial epithelial cells.⁶⁷

Bronchial epithelial cells are capable of producing a variety of cytokines and chemokines that may contribute to the initiation and perpetuation of airway inflammation. Several studies have shown that cytokine-induced expression of eotaxin, IL-6, IL-8, GM-CSF, and RANTES can be diminished by glucocorticoids *in vitro*.⁶⁸⁻⁷⁶ In contrast, glucocorticoids did not modulate the secretion of G-CSF by human bronchial epithelial cells.⁷⁶ *In vivo* studies have shown that treatment with inhaled steroids decreases both the expression of GM-CSF,⁷⁷ IL-1 β ,⁷⁸ IL-8,⁷⁹ and RANTES⁸⁰ by the bronchial epithelium, together with the number of activated eosinophils in the epithelium.

Receptors

Glucocorticoids may modulate the expression of several receptors. The expression of the neurokinin (NK)₁ receptor, which mediates many effects of substance P (SP) in the airways and is believed to be up-regulated in asthma,⁸¹ is down-regulated by glucocorticoids.⁸² Since the NK₁ receptor gene promoter region has no GRE but has an AP-1 response element, this effect probably will be mediated via an interaction of the glucocorticoid-GR complex with AP-1.

In contrast to NK₁ receptors, expression of the β_2 -adrenergic receptor is increased by glucocorticoids.⁸³ Since the human β_2 -adrenergic receptor gene contains three potential GRE, this effect of glucocorticoids probably is a direct one.⁸³ Up-regulation of β_2 -adrenergic receptors by glucocorticoids may be relevant in asthma as it may prevent down-regulation in response to prolonged treatment with β_2 -agonists.⁸⁴

The IL-1 receptor type II, which functions as a decoy receptor,⁸⁵ may also be up-regulated by glucocorticoids, thereby reducing the functional activity of IL-1 agonists.^{86,87} Soluble TNF-receptor type I (p55) release by human bronchial epithelial cells, both constitutive as well as IL-1 β -induced, has been shown to be reduced by glucocorticoids.⁸⁸ In contrast, glucocorticoids up-regulate the expression of IL-6 receptors in rat hepatoma and human epithelial cells.^{89,90} Thus far little is known about this process in human bronchial epithelial cells, which constitutively express these receptors.⁹¹

Glucocorticoids also modulate the expression of their own receptor. In a recent study it was shown that expression of the α -form (but not the β -form) of the GR in human bronchial epithelial cells was down-regulated in healthy subjects after 4 weeks of budesonide inhalation.²³

Enzymes

Glucocorticoids inhibit the synthesis of several inflammatory mediators implicated in the pathogene-

sis of asthma through an inhibitory effect on enzyme induction. The synthesis of inducible nitric oxide synthase (iNOS) by human airway epithelial cells is inhibited by glucocorticoids, both *in vitro* and *in vivo*.⁹²⁻⁹⁴ This effect seems to be mediated via inactivation of NF- κ B.^{95,96} Since nitric oxide (NO) may contribute to skewing of Th lymphocytes towards a Th2 phenotype, thereby promoting IgE production and eosinophil recruitment, inhibition of iNOS may be of importance in anti-inflammatory therapy in asthma.⁹⁷

Glucocorticoids also inhibit the gene transcription of a cytosolic form of phospholipase A₂ induced by cytokines⁹⁸ and inhibit the gene expression of cyclooxygenase-2, resulting in reduced formation of prostaglandins and thromboxanes.⁹⁹

In contrast to the enzymes mentioned above, glucocorticoids have been shown to increase the expression of neutral endopeptidase (NEP),¹⁰⁰⁻¹⁰² thereby potentially limiting neurogenic inflammatory responses.¹⁰³ In accordance with these results, it was found that the expression of NEP on bronchial epithelial cells was higher in asthmatics treated with steroids compared with nonsteroid-treated asthmatics.¹⁰⁴

Endothelins

Endothelins are a family of highly homologous 21-amino acid peptides, characterized by two intrachain disulphide chains, a hairpin loop consisting of polar amino acids, and a hydrophobic C-terminal chain.¹⁰⁵ Human bronchial epithelial cells have been shown to produce ET-1,¹⁰⁶⁻¹⁰⁸ which promotes the proliferation of smooth muscle cells, is a potent constrictor of both vascular and non-vascular smooth muscle cells, increases the secretion of mucus, and may activate inflammatory cells.^{105,107,109} ET-1 also stimulates collagen gene expression and through its inhibitory actions on collagenase will promote airway wall collagen deposition, thereby contributing to airway wall thickening which underlies bronchial hyperresponsiveness.¹¹⁰⁻¹¹² Increased levels of ET-1-immunoreactivity were detected in airway epithelium and vascular endothelium of bronchial biopsy specimens from nonsteroid-treated asthmatics compared with healthy subjects.^{106,113,114} In contrast, no increased ET-1 expression was found in the bronchial epithelium of asthmatic patients treated with glucocorticoids.¹¹⁵

Adhesion molecules

Adhesion molecules play an important role in the recruitment of inflammatory cells to the inflammatory locus. Expression of adhesion molecules on endothelial, epithelial or inflammatory cells is often

induced by cytokines, whereas glucocorticoids reduce surface expression of adhesion molecules. This effect may be due either to inhibition of cytokine synthesis or to a direct effect of glucocorticoids on adhesion molecule gene transcription. It has been shown that the expression of ICAM-1, endothelial leukocyte adhesion molecule (ELAM)-1, and E-selectin is down-regulated by steroids.¹¹⁶ Basal and cytokine-stimulated ICAM-1 expression on human bronchial epithelial cell lines is inhibited by glucocorticoids.^{117,118} However, inhaled glucocorticoids did not modulate ICAM-1 expression by bronchial epithelial cells from asthmatics *in vivo*.¹¹⁹

Eosinophil adhesion to cytokine-stimulated bronchial epithelial cells was shown to be inhibited by the synthetic glucocorticoid dexamethasone.¹²⁰ Although cytokine-activated epithelial cells showed increased expression of ICAM-1, this molecule did not seem to be involved in the decreased adhesion of eosinophils observed in the presence of dexamethasone.¹²⁰

Inhibitory proteins

The anti-inflammatory effects of glucocorticoids may be mediated by increasing the production of inhibitory proteins, such as lipocortins. Lipocortins are members of a superfamily of proteins characterized by their ability to bind calcium and anionic phospholipids, now known as the 'annexins'.^{121,122} In several cell types, but not all, glucocorticoids are inducers of lipocortins, which have an inhibitory effect on the activity of phospholipase A₂.^{123,124} As a result, the synthesis of lipid mediators, including prostaglandins and eicosanoids, will be reduced. However, in human bronchial epithelial cells glucocorticoids do not seem to up-regulate the expression of lipocortins.¹²⁵ Furthermore, no significant difference was found between lipocortin-1 concentration in BAL fluid from asthmatic patients receiving inhaled glucocorticoid therapy and those who were not treated with glucocorticoids.¹²⁶

Recently, glucocorticoids have also been shown to increase the expression of intracellular IL-1 receptor antagonist type I by human bronchial epithelial cells *in vitro*.¹²⁷ Increased production of this mediator may inhibit the effects of IL-1 agonists, thereby reducing inflammation. However, glucocorticoid treatment of asthmatic patients did not affect the expression of IL-1 receptor antagonist by the bronchial epithelium.⁷⁸

To provide protection against potentially injurious agents, airway epithelial cells secrete a number of mediators, including antiproteases. Secretory leukocyte protease inhibitor (SLPI) is the predominant antiprotease in the airways. Its expression has been shown to be increased in airway epithelial cells after stimulation with glucocorticoids.¹²⁸

Cellular and Clinical Effects of Glucocorticoids in Asthma

Several studies have determined the effects of inhaled glucocorticoids on bronchial inflammation, either by measurements in BAL fluid, sputum, or exhaled air, or by performing bronchial biopsies. Although differences can be observed between different trials, these studies have confirmed that glucocorticoid treatment of asthmatic patients reduces the number and activation of inflammatory cells in the airways, together with an improvement of lung function. Nowadays, the potent anti-inflammatory actions of glucocorticoids are thought to underlie the clinical efficacy of oral glucocorticoids.¹²⁹

Effects of glucocorticoids on immunopathology

Inhaled glucocorticoids decrease the number and activation status of most inflammatory cells in the bronchus, including mast cells, dendritic cells, eosinophils, and T lymphocytes. Changes in cellular infiltration are accompanied by modulated expression of several cytokines. Inhaled glucocorticoids have been shown to decrease mRNA expression of GM-CSF, IL-13, IL-4, and IL-5, whereas mRNA levels of IL-12 and IFN- γ increased, suggesting a shift from a Th2 towards a more Th1-like environment.^{77,130,131}

Glucocorticoid treatment is associated with a reduction in *mast cell* numbers in the bronchus^{79,129,132-135} and with reduced mast cell associated mediators in BAL fluid.^{135,136} This may be due to a reduction in IL-3 and stem cell factor production, which are necessary for the survival of mast cells in tissue. The (IgE-dependent) release of mediators from mast cells does not seem to be affected by glucocorticoid treatment.^{137,138}

Dendritic cells play an important role in presenting antigens to (naive) T cells.^{139,140} Inhaled glucocorticoids have been shown to reduce the number of dendritic cells in the human bronchial epithelium.¹⁴¹

Increased numbers of eosinophils are a prominent feature of asthmatic airways.¹⁴²⁻¹⁴⁸ *In vitro* studies have shown that many eosinophil functions, including adherence and chemotaxis, are diminished following glucocorticoid treatment.¹³⁸ However, most data suggest that eosinophil responses to steroids are likely to be indirect, since eosinophil function is markedly affected by cytokines elaborated from T lymphocytes (IL-3, IL-4, IL-5, GM-CSF), endothelial cells (GM-CSF) and epithelial cells (GM-CSF).¹⁴⁹⁻¹⁵³ *In vivo* studies indicate that treatment with inhaled steroids reduces the number of eosinophils and eosinophil-related mediators in BAL fluid^{79,148,154} and the number of (activated) eosinophils in bronchial biopsies.^{79,129,132,133,155} Recently, induced sputum has been suggested as a useful tool for evaluating the

effects of therapy on airway mucosal inflammation. Thus far, most studies have focused on the presence of eosinophils and eosinophil-related mediators. In accordance with the findings in BAL fluid and bronchial biopsies, glucocorticoid treatment was associated with a reduction in sputum eosinophil numbers, eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO).¹⁵⁶

Glucocorticoids also reduce the number of activated T lymphocytes in bronchial biopsies and BAL fluid.^{129,133,134,155,157} In addition, inhaled corticosteroids reduced the number of cells expressing mRNA for IL-4 or IL-5, and increased the number of cells expressing mRNA for IFN- γ ,^{131,132} thereby favouring the development of Th1 cells.¹⁵⁸

In addition to the effects of glucocorticoids on epithelial cells described above, inhaled glucocorticoid therapy has been shown to reduce the shedding of epithelial cells.^{155,159,160} No consistent effect of corticosteroids on the thickness of the basement membrane has been observed.^{79,160,161}

Besides the suppressive effects on inflammatory cells, inhaled glucocorticoids have also shown to inhibit mucus secretion and microvascular leakage (as determined by the down-regulation of plasma proteins in BAL fluid).^{160,162-166} At present it is not clear whether this is mediated via a direct effect of glucocorticoids on endothelial or mucous cells, or via a reduction of inflammatory mediators that increase mucus secretion and vascular leakage.

Effects of glucocorticoids on lung function

Treatment with glucocorticoids has been consistently shown not only to reduce the symptoms of asthma, but also bronchial hyperresponsiveness.^{134,167-169} In contrast to the rapid inhibitory effects of β_2 -agonists, glucocorticoids given in a single dose are not effective in preventing early allergen-invoked bronchoconstriction, but inhibition of the late response has been clearly demonstrated.^{170,171} In contrast, chronic treatment with either oral or inhaled steroids attenuates even the early bronchoconstriction to allergen,¹⁷¹⁻¹⁷³ an effect that probably is mediated via the anti-inflammatory actions of glucocorticoids already described. Although inhaled glucocorticoids consistently reduce airway hyperreactivity in asthmatics,¹⁶⁹ even after several months of treatment responsiveness fails to return to the normal range. This may reflect persistence of structural changes that cannot be reversed by steroids (such as the thickening of the basement membrane), despite of suppression of the inflammatory and immunological processes.

Concluding Remarks

Glucocorticoids are widely used in the treatment of asthma and have anti-inflammatory effects. These

effects are mediated either by direct binding of the glucocorticoid/GR complex to GRE in the promoter region of responsive genes, or by an interaction of this complex with transcription factors such as AP-1 and NF- κ B. Glucocorticoids inhibit the expression of a large number of inflammation-associated molecules, including cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules. These effects predominantly are mediated via inhibition of NF- κ B activity. In contrast, anti-inflammatory mediators, such as NEP and IL-1 receptor antagonist, often are up-regulated by glucocorticoids. The beneficial effects of glucocorticoid therapy in asthma is demonstrated by *in vivo* studies showing that treatment of asthmatic patients with inhaled glucocorticoids inhibits the inflammation of the airways and simultaneously improves their lung function. These effects may be mediated in part by modulation of epithelial cell functions, since many studies, both *in vitro* and *in vivo*, have shown that glucocorticoids are able to modulate the inflammatory functions of bronchial epithelial cells. Further studies on the mechanism of action of glucocorticoids will eventually lead to the development of drugs which specifically inhibit the transcription of inflammatory genes without having negative side effects, and will contribute to a more efficient treatment of asthmatic patients.

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