

Allergy Review Series VII: Intracellular signaling and regulation of allergic reactions

Molecular mechanisms of corticosteroids in allergic diseases

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Accepted for publication 2 April 2001
Review Series VII Editor: Prof. M. Kowalski

Corticosteroids are by far the most effective therapy currently available for allergic diseases, such as asthma. We now have a much better understanding of the molecular mechanisms whereby corticosteroids suppress inflammation in allergic diseases.

Molecular mechanisms

Corticosteroids are a highly effective anti-inflammatory therapy in allergy, and the molecular mechanisms involved in the suppression of allergic inflammation are now better understood (1). Corticosteroids are effective clinically because they block many of the inflammatory pathways that are abnormally activated in allergic diseases, and they have a very wide spectrum of anti-inflammatory actions.

Glucocorticoid receptors (GR)

Corticosteroids bind to a single class of glucocorticoid receptor (GR) that is localized to the cytoplasm of target cells. Corticosteroids bind at the C-terminal end of the receptor, whereas the N-terminal end of the receptor is involved in gene transcription. Between these domains is the DNA-binding domain, which has two finger-like projections, formed by a zinc molecule bound to four cysteine residues, that bind to the DNA double helix. The inactive GR is bound to a protein complex that includes two molecules of the 90-kDa heat-shock protein (hsp90) and various other proteins that act as “molecular chaperones” to prevent the unoccupied GR from moving into the nuclear compartment. Once corticosteroids bind to GR, conformational changes in the receptor structure result in

dissociation of these chaperone molecules, thereby exposing nuclear localization signals on GR, and resulting in rapid nuclear localization of the activated GR-corticosteroid complex and its binding to DNA (Fig. 1). Two GR molecules bind to DNA as a dimer, resulting in changed transcription. A splice variant of GR, termed GR- β , has been identified that does not bind corticosteroids, but does bind to DNA, and theoretically may interfere with the action of corticosteroids by blocking GRE binding (2).

Increased gene transcription

Corticosteroids produce their effect on responsive cells by activating GR to regulate directly or indirectly the transcription of certain target genes (3). 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 interacting with a large coactivator molecule, CREB-binding protein (CBP). CBP is bound at the start site of transcription, and this leads via a series of linking proteins to the binding and activation of RNA polymerase II, resulting in the formation of messenger RNA (mRNA) and then synthesis of protein. Binding of activated GR to CBP

results in increased acetylation of core histones around which DNA is wound within the chromosomal structure (4), and this is critical for the subsequent activation of RNA polymerase II. For example, high concentrations of corticosteroids increase the secretion of the antiprotease secretory leukoprotease inhibitor (SLPI) from epithelial cells. This is associated with a selective acetylation of lysine residues 5 and 16 on histone 4, resulting in increased gene transcription.

Decreased gene transcription

In controlling inflammation, the major effect of corticosteroids is to inhibit the synthesis of inflammatory proteins. This was originally believed to be through the interaction of GR with negative GREs, resulting in repression of transcription. However, negative GREs have only very rarely been demonstrated and are not a feature of the promoter region of inflammatory genes that are suppressed by steroids in the treatment of allergic diseases.

Interaction with transcription factors

Activated GRs may bind directly to several other activated transcription factors as a protein–protein interaction. This could be an important determinant of corticosteroid responsiveness, and it is a key mechanism whereby corticosteroids switch off inflammatory genes. Most of the inflammatory genes that are activated in asthma do not appear to have GREs in their promoter regions, and yet they are repressed by corticosteroids. There is persuasive evidence that corticosteroids inhibit the effects of the transcription factors that regulate the expression of genes that code for inflammatory proteins, such as cytokines, inflammatory enzymes, adhesion molecules, and inflammatory receptors. These “inflammatory” transcription factors include activator protein-1 (AP-1) and nuclear factor- κ B (NF- κ B), which may regulate many of the inflammatory genes that are switched on in asthmatic airways (5, 6). It was once believed that the activated GR interacted directly with activated transcription factors through a protein–protein interaction, but this may be a feature of transfected cells, rather than of primary cells. Thus, in a chronically transfected epithelial cell line with a NF- κ B-driven reporter gene, there is relatively little effect of corticosteroids on transcription (7). Furthermore, treatment of asthmatic patients with high doses of inhaled corticosteroids that suppress airway inflammation is not associated with any reduction in NF- κ B binding to DNA (8). This suggests that corticosteroids act downstream of the binding of proinflammatory transcription factors to DNA, and attention has now focused on their effects on chromatin structure and histone acetylation.

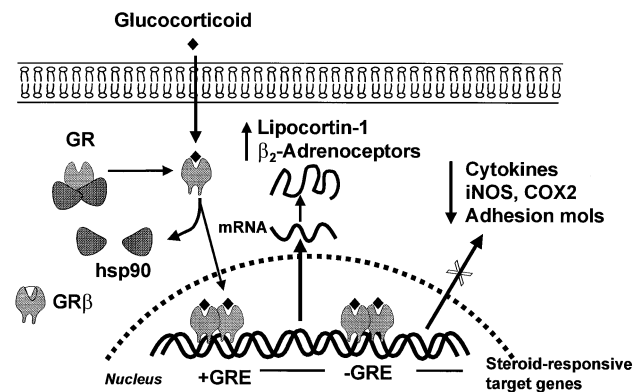


Figure 1. Classical model of corticosteroid action. Corticosteroids enter the cell and bind to cytoplasmic glucocorticoid receptors (GR) that are complexed with two molecules of a 90-kDa heat-shock protein (hsp90). GR translocates to the nucleus, where, as a dimer, it binds to a glucocorticoid recognition element (GRE) on the 5'-upstream promoter sequence of steroid-responsive genes. GREs increase transcription, whereas negative GREs (nGREs) may decrease transcription, resulting in increased or decreased messenger RNA (mRNA) and protein synthesis. An isoform of GR, GR- β , binds to DNA but is not activated by corticosteroids.

Effects on chromatin structure

There is increasing evidence that corticosteroids may have effects on the chromatin structure. DNA in chromosomes is wound around histone molecules in the form of nucleosomes (9, 10). Several transcription factors interact with large coactivator molecules, such as CBP and the related molecule p300, which bind to the basal transcription factor apparatus. Several transcription factors bind directly to CBP, including AP-1, NF- κ B, STATs, and GR (11, 12) (Fig. 2). At the microscopic level, the chromatin may become dense or opaque due to the winding or unwinding of DNA around the histone core. Coactivator molecules, including CBP and the related p300, have histone acetylation activity that is stimulated by the binding of transcription factors, such as AP-1 and NF- κ B. Acetylation of lysine residues in the N-terminal tails of core histones results in the unwinding of DNA that is tightly coiled around the histone core of the resting gene, thus opening up the chromatin structure. This allows transcription factors and RNA polymerase to bind more readily, thereby switching on or increasing transcription.

The repression of genes reverses this process by deacetylation of the acetylated histone residues (13). Deacetylation of histones increases the winding of DNA around histone residues, resulting in dense chromatin structure and reduced access of transcription factors and RNA polymerase to their binding sites, and thereby leading to repressed transcription of inflammatory genes. Activated GR may bind to several transcription corepressor molecules that associate with proteins that have histone deacetylase (HDAC) activity,

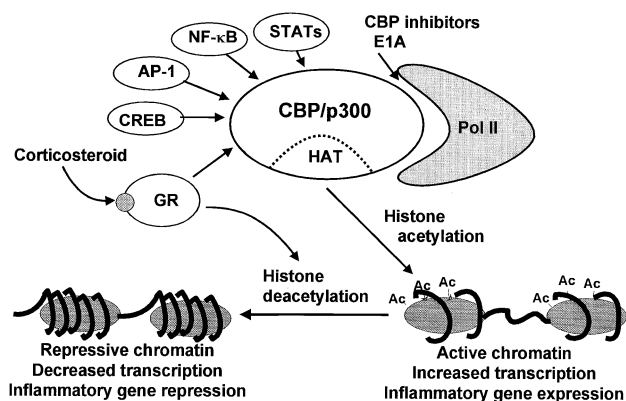


Figure 2. Effect of corticosteroids on chromatin structure. Transcription factors, such as STATs, AP-1, and NF- κ B, bind to coactivator molecules, such as CREB-binding protein (CBP) or p300, which have intrinsic histone acetyltransferase (HAT) activity, resulting in acetylation (-Ac) of histone residues. This leads to unwinding of DNA and allows increased binding of transcription factors, resulting in increased gene transcription. After activation by corticosteroids, glucocorticoid receptors (GR) bind to a glucocorticoid receptor coactivator, which is bound to the CBP. This results in deacetylation of histone, with increased coiling of DNA around histone, thus preventing transcription factor binding that leads to gene repression.

resulting in deacetylation of histone, increased winding of DNA around histone residues, and thus reduced access of transcription factors to their binding sites and therefore repression of inflammatory genes. In addition, activated GR recruits HDACs to the transcription start site, resulting in deacetylation of histones, and a decrease in inflammatory gene transcription (4). Several distinct HDACs are now recognized, and these are differentially expressed and regulated in different cell types (14). This may contribute to the differences in responsiveness to corticosteroids between different genes and cells.

Nontranscriptional effects

It is increasingly recognized that GR may also affect the synthesis of some proteins by reducing the stability of mRNA, through effects on the ribonucleases that break down mRNA. Some inflammatory genes, such as the gene encoding GM-CSF, produce mRNA that has a sequence rich in AU nucleotides at the 3'-untranslated end. It is this region that interacts with the ribonucleases that break down mRNA, thus switching off protein synthesis (15).

Target genes in allergic inflammation control

Corticosteroids may control inflammation by inhibiting many aspects of the inflammatory process in allergy through increasing the transcription of anti-inflammatory genes and decreasing the transcription of inflammatory genes (Table 1).

Anti-inflammatory proteins

Corticosteroids may suppress inflammation by increasing the synthesis of anti-inflammatory proteins. For example, corticosteroids increase the synthesis of lipocortin-1, a 37-kDa protein that has an inhibitory effect on phospholipase A₂ (PLA₂), and therefore may inhibit the production of lipid mediators. Corticosteroids induce the formation of lipocortin-1 in several cells, and recombinant lipocortin-1 has acute anti-inflammatory properties. However, lipocortin-1 does not appear to be increased by inhaled corticosteroid treatment in asthma (16). Corticosteroids increase the expression of other potentially anti-inflammatory proteins, such as interleukin (IL)-1 receptor antagonist (which inhibits the binding of IL-1 to its receptor), SLPI (which inhibits proteases, such as tryptase), neutral endopeptidase (which degrades bronchoactive peptides such as kinins), CC-10 (an immunomodulatory protein), the inhibitor of NF- κ B (I κ B- α), and IL-10 (an anti-inflammatory cytokine). The expression of IL-10 in macrophages from asthmatic patients is decreased, and this may increase the expression of several inflammatory genes. Corticosteroids increase secretion of IL-10 and may therefore overcome this defect (17).

β_2 -Adrenoceptors

Corticosteroids increase the expression of β_2 -adrenoceptors by increasing the rate of transcription and the human β_2 -receptor gene has three potential GREs (18). Corticosteroids double the rate of β_2 -receptor gene transcription, in human lung *in vitro*, resulting in increased expression of β_2 -receptors (19). This also occurs *in vivo* in nasal mucosa after treatment with topical corticosteroids (20). This may be relevant in asthma, as corticosteroids may prevent downregulation of β -receptors in response to prolonged treatment with β_2 -agonists. In rats, corticosteroids prevent downregulation and reduced transcription of β_2 -receptors in response to chronic exposure to β -agonists (21).

Cytokines

The inhibitory effect of corticosteroids on cytokine synthesis is likely to be of particular importance in the control of inflammation in allergic inflammation, as cytokines play a critical role in the chronic inflammatory process (22). Corticosteroids inhibit the transcription of many cytokines and chemokines that are relevant in allergy (Table 1). These inhibitory effects are due, at least in part, to an inhibitory effect on the transcription factors that regulate induction of these cytokine genes, including AP-1 and NF- κ B. For example, eotaxin, which is important in selective attraction of eosinophils from the circulation into the airways, is regulated in part by NF- κ B, and its

Table 1. Effect of corticosteroids on gene transcription

<i>Increased transcription</i>	
Lipocortin-1 (phospholipase A ₂ inhibitor)	
β ₂ -Adrenoceptor	
Secretory leukoprotease inhibitor	
Clara cell protein (CC10, phospholipase A ₂ inhibitor)	
IL-1 receptor antagonist	
IL-1R2 (decoy receptor)	
IκB-α (inhibitor of NF-κB)	
<i>Decreased transcription</i>	
<i>Cytokines</i>	
(IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-11, IL-12, IL-13, IL-16, IL-17, IL-18, TNF-α, GM-CSF, SCF)	
<i>Chemokines</i>	
(IL-8, RANTES, MIP-1α, MCP-1, MCP-3, MCP-4, eotaxin)	
Inducible nitric oxide synthase (iNOS)	
Inducible cyclooxygenase (COX-2)	
Cytoplasmic phospholipase A ₂ (cPLA ₂)	
Endothelin-1	
NK ₁ -receptors, NK ₂ -receptors	
Adhesion molecules (ICAM-1, E-selectin)	

expression in airway epithelial cells is inhibited by corticosteroids (23). Many transcription factors, in addition to AP-1 and NF-κB, are likely to be involved in the regulation of inflammatory genes in asthma. IL-4 and IL-5 expression in T cells plays a critical role in allergic inflammation, but NF-κB does not play a role, whereas the transcription factor nuclear factor of activated T cells (NF-AT) is important (24). AP-1 is a component of the NF-AT transcription complex, so that corticosteroids inhibit IL-5, at least in part, by inhibiting the AP-1 component of NF-AT.

There may be marked differences in the response of different cells and of different cytokines to the inhibitory action of corticosteroids, and these differences may depend on the relative abundance of transcription factors within different cell types. Thus, in alveolar macrophages and peripheral blood monocytes, GM-CSF secretion is more potently inhibited by corticosteroids than IL-1β or IL-6 secretion (25).

Inflammatory enzymes

Nitric oxide (NO) synthase may be induced by pro-inflammatory cytokines, resulting in NO production. NO may amplify asthmatic inflammation and contribute to epithelial shedding and airway hyperresponsiveness (AHR) through the formation of peroxynitrite. The induction of the inducible form of NOS (iNOS) is inhibited by corticosteroids. In cultured human pulmonary epithelial cells, proinflammatory cytokines result in increased expression of iNOS and increased NO formation, due to increased transcription of the iNOS gene, and this is inhibited by corticosteroids acting partly through inhibition of NF-κB (26). Corticosteroids inhibit the synthesis of several other

inflammatory mediators implicated in asthma through an inhibitory effect on the induction of enzymes, such as cyclooxygenase-2 and cytosolic PLA₂ (27).

Inflammatory receptors

Corticosteroids also decrease the transcription of genes coding for certain receptors. Thus, the gene for the NK₁-receptor, which mediates the inflammatory effects of tachykinins in the airways, has an increased expression in asthma and is inhibited by corticosteroids, probably via an inhibitory effect on AP-1 (28). Corticosteroids also inhibit the transcription of the NK₂-receptor, which mediates the bronchoconstrictor effects of tachykinins (29). Corticosteroids also inhibit the expression of the inducible bradykinin B₁-receptor and bradykinin B₂-receptor (30).

Adhesion molecules

Adhesion molecules play a key role in the trafficking of inflammatory cells to sites of inflammation. The expression of many adhesion molecules on endothelial cells is induced by cytokines, and corticosteroids may lead indirectly to a reduced expression via their inhibitory effects on cytokines such as IL-1β and TNF-α. Corticosteroids may also have a direct inhibitory effect on the expression of adhesion molecules, such as ICAM-1 and E-selectin, at the level of gene transcription. ICAM-1 and VCAM-1 expression in bronchial epithelial cell lines and monocytes is inhibited by corticosteroids (31).

Apoptosis

Corticosteroids markedly reduce the survival of certain inflammatory cells, such as eosinophils. Eosinophil survival is dependent on the presence of certain cytokines, such as IL-5 and GM-CSF. Exposure to corticosteroids blocks the effects of these cytokines and leads to programmed cell death, or apoptosis, although the corticosteroid-sensitive molecular pathways have not yet been defined (32). By contrast, corticosteroids decrease apoptosis in neutrophils and thus prolong their survival (33). This may contribute to the lack of anti-inflammatory effects of corticosteroids in chronic obstructive pulmonary disease (COPD), in which neutrophilic inflammation is predominant.

Effects on cell function

Corticosteroids may have direct inhibitory actions on several inflammatory cells and structural cells that are implicated in asthma (Fig. 3).

Macrophages

Corticosteroids inhibit the release of inflammatory mediators and cytokines from alveolar macrophages

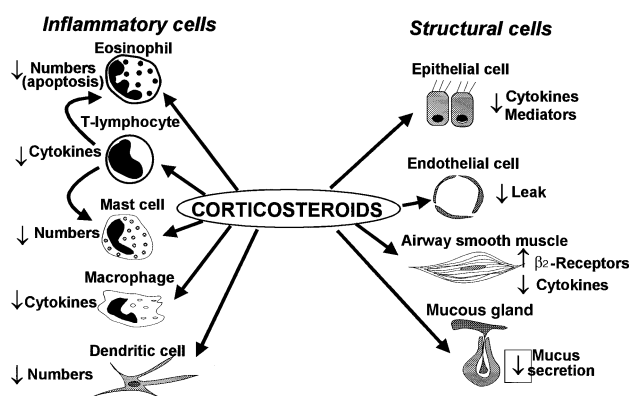


Figure 3. Cellular effect of corticosteroids.

in vitro (25). Inhaled corticosteroids reduce the secretion of chemokines and proinflammatory cytokines from alveolar macrophages in asthmatic patients, whereas the secretion of IL-10 is increased (17).

Eosinophils

Corticosteroids have a direct inhibitory effect on mediator release from eosinophils, although they are only weakly effective in inhibiting the secretion of reactive oxygen species and eosinophil basic proteins. More importantly, corticosteroids induce apoptosis by inhibiting the prolonged survival due to IL-3, IL-5, and GM-CSF (32, 33), resulting in an increased number of apoptotic eosinophils in the induced sputum of asthmatic patients (34). In asthma, there is a delay in the apoptosis of eosinophils, which is reversed by treatment with corticosteroids (35). One of the best described actions of corticosteroids in asthma is a reduction in circulating eosinophils, an effect which may reflect an action on eosinophil production in the bone marrow.

T cells

T helper 2 cells (Th2) play an important orchestrating role in asthma through the release of the cytokines IL-4, IL-5, IL-9, and IL-13, and they may be an important target for corticosteroids in asthma therapy. Corticosteroids also induce apoptosis in T cells.

Mast cells

While corticosteroids do not appear to have a direct inhibitory effect on mediator release from lung mast cells, chronic corticosteroid treatment is associated with a marked reduction in the numbers of mucosal mast cells. This may be linked to a reduction in the production of IL-3 and stem-cell factor (SCF), which are necessary for mast-cell expression at mucosal surfaces. Mast cells also secrete various cytokines (TNF- α , IL-4, IL-5, IL-6, and IL-8), and this may also be inhibited by corticosteroids (36).

Dendritic cells

Dendritic cells in the epithelium of the respiratory tract appear to play a critical role in antigen presentation in the lung, as they have the capacity to take up allergen, process it into peptides, and present it, via MHC molecules on the cell surface, to uncommitted T cells. In experimental animals, the number of dendritic cells is markedly reduced by systemic and inhaled corticosteroids, thus dampening the immune response in the airways (37).

Neutrophils

Neutrophils, which are not prominent in the biopsies of asthmatic patients, are not sensitive to the effects of corticosteroids. Indeed, systemic corticosteroids increase peripheral neutrophil counts, a fact which may reflect an increased survival time due to an inhibitory action on neutrophil apoptosis (33).

Endothelial cells

GR gene expression in the airways is most prominent in endothelial cells of the bronchial circulation and airway epithelial cells. Corticosteroids do not appear to inhibit directly the expression of adhesion molecules, although they may inhibit cell adhesion indirectly by suppression of cytokines involved in the regulation of adhesion molecule expression. Corticosteroids may have an inhibitory action on airway microvascular leakage induced by inflammatory mediators. This appears to be a direct effect on postcapillary venular epithelial cells. Although there have been no direct measurements of the effects of corticosteroids on airway microvascular leakage in asthmatic airways, regular treatment with inhaled corticosteroids decreases the elevated plasma proteins found in the bronchoalveolar lavage fluid of patients with stable asthma.

Epithelial cells

Epithelial cells may be an important source of many inflammatory mediators in asthmatic airways and may drive and amplify the inflammatory response in the airways through the secretion of proinflammatory cytokines, chemokines, and inflammatory peptides. Airway epithelium may be one of the most important cellular targets for inhaled corticosteroids in asthma (38, 39). Inhaled corticosteroids inhibit the increased expression of many inflammatory proteins in airway epithelial cells. An example is iNOS, which has an increased expression in airway epithelial and inflammatory cells in asthma, and which is reduced by inhaled corticosteroids (40). This is reflected by a reduction in the elevated levels of exhaled NO in asthma after the administration of inhaled corticosteroids (41).

Mucus secretion

Corticosteroids inhibit mucus secretion in airways, and this may be a direct action of corticosteroids on submucosal gland cells. Corticosteroids may also inhibit the expression of mucin genes, such as MUC2 and MUC-5AC (42). In addition, there are indirect inhibitory effects due to the reduction in inflammatory mediators that stimulate increased mucus secretion.

Effects on allergic inflammation

Corticosteroids are remarkably effective in controlling the inflammation in asthma, rhinitis, and atopic dermatitis, and it is likely that they have multiple cellular effects. Biopsy studies in patients with asthma have now confirmed that inhaled corticosteroids reduce the number and activation of inflammatory cells in the airway mucosa and in bronchoalveolar lavage (38). These effects may be due to inhibition of cytokine synthesis in inflammatory and structural cells and suppression of adhesion molecules. The disrupted epithelium is restored, and the ratio of ciliated cells to goblet cells is normalized after 3 months of therapy with inhaled corticosteroids. There is also some evidence for a reduction in the thickness of the basement membrane, although in asthmatic patients taking inhaled corticosteroids for over 10 years the characteristic thickening of the basement membrane is still present.

Effects on airway hyperresponsiveness (AHR)

By reducing airway inflammation, inhaled corticosteroids consistently reduce AHR in asthmatic adults and children (43). Chronic treatment with inhaled corticosteroids reduces responsiveness to histamine, cholinergic agonists, allergen (early and late responses), exercise, fog, cold air, bradykinin, adenosine, and irritants (such as sulphur dioxide and metabisulphite). The reduction in AHR takes place over several weeks and may not be maximal until several months of therapy. The magnitude of reduction is variable between patients, is in the order of one to two doubling dilutions for most challenges, and often fails to return to the normal range. This may reflect suppression of the inflammation but also the persistence of structural changes that cannot be reversed by corticosteroids. Inhaled corticosteroids not only make the airways less sensitive to spasmogens but also limit the maximal airway narrowing in response to spasmogens.

Corticosteroid resistance

Although corticosteroids are highly effective in the control of asthma and other chronic inflammatory or immune diseases, a small proportion of patients with asthma fail to respond even to high doses of oral

corticosteroids (44–46). Resistance to the therapeutic effects of corticosteroids is also recognized in other inflammatory and immune diseases, including rheumatoid arthritis and inflammatory bowel disease. Corticosteroid-resistant patients, although uncommon, present considerable management problems. Recently, new insights into the mechanisms whereby corticosteroids suppress chronic inflammation have shed new light on the molecular basis of corticosteroid-resistant asthma.

Corticosteroid-resistant asthma is defined as a failure to improve FEV₁ or PEF by over 15% after treatment with oral prednisolone 30–40 mg daily for 2 weeks, providing that the oral steroid is taken (verified by plasma prednisolone level or a reduction in early-morning cortisol level). These patients are not Addisonian, and they do not suffer from the abnormalities in sex hormones described in the very rare familial glucocorticoid resistance. Plasma cortisol and adrenal suppression in response to exogenous cortisol is normal in these patients, so they suffer from the side-effects of corticosteroids.

Complete corticosteroid resistance in asthma is very rare, with a prevalence of <1:1000 asthmatic patients. Much more common is a reduced responsiveness to corticosteroids, so that large inhaled or oral doses are needed to control asthma adequately (corticosteroid-dependent asthma). It is likely that there is a range of responsiveness to corticosteroids and that corticosteroid resistance is at one extreme of this range.

It is important to establish that the patient has asthma, rather than COPD, “pseudoasthma” (a hysterical conversion syndrome involving vocal cord dysfunction), left ventricular failure, or cystic fibrosis that does not respond to corticosteroids. Asthmatic patients are characterized by a variability in PEF and, in particular, a diurnal variability of over 15% and episodic symptoms. It is also important to identify provoking factors (allergens, drugs, or psychological problems) that may increase the severity of asthma and its resistance to therapy. Biopsy studies have demonstrated the typical eosinophilic inflammation of asthma in these patients (45).

Molecular mechanisms of corticosteroid resistance

There may be several mechanisms for resistance to the effects of corticosteroids. Certain cytokines (particularly IL-2, IL-4, and IL-13) may induce a reduction in affinity of GR in inflammatory cells such as T cells, resulting in local resistance to the anti-inflammatory actions of corticosteroids (45). Another mechanism is an increased activation of the transcription factor AP-1 by inflammatory cytokines, so that AP-1 may consume activated GR and thus reduce their availability for suppression of inflammation at inflamed sites (47). There is an increased expression of c-Fos, one of the

components of AP-1 (48). The cause of this excessive activation of AP-1 by activating enzymes is currently unknown, but may be genetically determined. Another proposed mechanism is an increase in expression of GR- β , which then interferes with the DNA binding of GR (49), but any increase in GR- β is insufficient to account for reduced responsiveness to corticosteroids (50).

Corticosteroid resistance in COPD

Although inhaled corticosteroids are highly effective in asthma, they provide little benefit in COPD, despite the fact that airway and lung inflammation is present. This may indicate that the inflammation in COPD is not suppressed by corticosteroids, with no reduction in inflammatory cells, cytokines, or proteases in induced sputum even with oral corticosteroids (51, 52). Corticosteroids do not suppress neutrophilic inflammation in the airways, and corticosteroids may prolong the survival of neutrophils (53). There is some evidence that the airway inflammation in COPD is corticosteroid resistant, as corticosteroids have no inhibitory effect on inflammatory proteins, such as cytokines, that are normally suppressed by corticosteroids. This lack of response to corticosteroids may be explained in part by an inhibitory effect of cigarette smoking on HDACs, thus interfering with an important anti-inflammatory action of corticosteroids (54).

Therapeutic implications

Inhaled corticosteroids are now used as first-line therapy for the treatment of persistent asthma in adults and children in many countries, as they are the most effective treatment for asthma currently available (55). They are also used widely for the treatment of perennial and seasonal rhinitis.

Dissociated corticosteroids

All currently available inhaled corticosteroids are

absorbed from the lungs into the systemic circulation and therefore inevitably have some systemic component. Understanding the molecular mechanisms of action of corticosteroids has led to the development of a new generation of corticosteroids. As discussed above, a major mechanism of the anti-inflammatory effect of corticosteroids appears to be inhibition of transcription factors, such as NF- κ B and AP-1, that are activated by proinflammatory cytokines (transrepression) via an inhibitory action on histone acetylation and stimulation of histone deacetylation. By contrast, the endocrine and metabolic effects of steroids that are responsible for the systemic side-effects of corticosteroids are likely to be mediated via DNA binding (transactivation). This has led to a search for novel corticosteroids that selectively transrepress, thus reducing the potential risk of systemic side-effects. Since corticosteroids bind to the same GR, this seems at first to be unlikely, but while DNA binding involves a GR homodimer, interaction with the transcription factors AP-1 and NF- κ B involves only a single GR. A separation of transactivation and transrepression has been demonstrated with reporter gene constructs in transfected cells by selective mutations of the GR. Furthermore, some steroids, such as the antagonist RU486, have a greater transrepression than transactivation effect. Indeed, the topical steroids used in asthma therapy today, such as fluticasone propionate (FP) and budesonide, appear to have more potent transrepression than transactivation effects, which may account for their selection as potent anti-inflammatory agents (56). Recently, a novel class of steroids has been described in which there is potent transrepression with relatively little transactivation. These "dissociated" steroids, including RU24858 and RU40066, have anti-inflammatory effects *in vitro* (57), although there is little separation of anti-inflammatory effects and systemic side-effects *in vivo* (58). This suggests that the development of steroids with a greater margin of safety is possible and may even lead to the development of oral steroids that do not have significant adverse effects.

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