Molecular Mechanisms and Cellular Effects of Glucocorticosteroids

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Glucocorticosteroids (GCSs) are widely used to treat various inflammatory and immune diseases. The most common use of GCSs today is in the treatment of asthma and other allergic diseases, and inhaled GCSs have now become established as first-line treatment in adults and children who have persistent asthma. There have been major advances in understanding the molecular mechanisms whereby corticosteroids suppress inflammation, based on recent developments in understanding the fundamental mechanisms of gene transcription [1,2]. This has important clinical implications, as it will lead to a better understanding of the inflammatory mechanisms of many diseases and may signal the development of new anti-inflammatory treatments in the future. The new understanding of these molecular mechanisms also helps to explain how corticosteroids are able to switch off multiple inflammatory pathways, and it also provides insights into why corticosteroids fail to work in patients who have steroid-resistant asthma and in patients who have chronic obstructive pulmonary disease (COPD).

The Molecular Basis of Inflammation in Allergic Diseases

Patients who have asthma and allergic rhinitis have a specific pattern of inflammation in the airways that is characterized by degranulated mast cells, infiltration of eosinophils, and increased number of activated T helper 2 (Th2) cells. Suppression of this inflammation by corticosteroids controls and prevents these symptoms in most patients. Multiple mediators are produced in allergic diseases and approximately 100 known inflammatory mediators that are increased include lipid mediators, inflammatory peptides, chemokines, cytokines,
and growth factors. There is increasing evidence that structural cells of the airways, such as epithelial cells, airway smooth muscle cells, endothelial cells, and fibroblasts are a major source of inflammatory mediators in asthma. Epithelial cells may play a particularly important role, as they may be activated by environmental signals and may release multiple inflammatory proteins, including cytokines, chemokines, lipid mediators, and growth factors.

Inflammation is mediated by the increased expression of multiple inflammatory proteins, including cytokines, chemokines, adhesion molecules, and inflammatory enzymes and receptors. Most of these inflammatory proteins are regulated by increased gene transcription, which is controlled by proinflammatory transcription factors, such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), that are activated in asthmatic airways [3]. For example, NF-κB is markedly activated in epithelial cells of patients who have asthma and this transcription factor regulates many of the inflammatory genes that are abnormally expressed in asthma. NF-κB may be activated by rhinovirus infection and allergen exposure, which exacerbate asthmatic inflammation.

**Chromatin remodeling**

Chromatin consists of DNA and basic proteins called histones, which provide the structural backbone of the chromosome. It has long been recognized that histones play a critical role in regulating the expression of genes and determines which genes are transcriptionally active and which ones are suppressed (silenced). The chromatin structure is highly organized, as almost 2 m of DNA have to be packed into each cell nucleus. Chromatin is made up of nucleosomes, which are particles consisting of 146 base pairs of DNA wound almost twice around an octomer of two molecules each of the core histone proteins H2A, H2B, H3, and H4. The important advance in the last decade has been to understand how expression and repression of genes is associated with remodelling of this chromatin structure by enzymatic modification of the core histone proteins, particularly by acetylation. Each core histone has a long N-terminal tail that is rich in lysine residues, which may become acetylated thus changing the electrical charge of the core histone. In the resting cell, DNA is wound tightly around core histones, excluding the binding of the enzyme RNA polymerase II, which activates gene transcription and the formation of messenger RNA. This conformation of the chromatin structure is described as closed and is associated with suppression of gene expression. Gene transcription only occurs when the chromatin structure is opened up, with unwinding of DNA so that RNA polymerase II and basal transcription complexes can now bind to DNA to initiate transcription.

**Histone acetyltransferases and coactivators**

When proinflammatory transcription factors such as NF-κB are activated they bind to specific recognition sequences in DNA and subsequently interact with
large coactivator molecules, such as cyclic AMP response element binding protein (CBP). These coactivator molecules act as the molecular switches that control gene transcription and all have intrinsic histone acetyltransferase (HAT) activity [4]. This activation results in acetylation of core histones, thereby reducing their charge, which allows the chromatin structure to transform from the resting closed conformation to an activated open form. This transformation results in unwinding of DNA, binding of TATA box binding protein (TBP), TBP-associated factors, and RNA polymerase II, which then initiates gene transcription. This molecular mechanism is common to all genes, including those involved in differentiation, proliferation, and activation of cells. This process is reversible and deacetylation of acetylated histones is associated with gene silencing. This deacetylation is mediated by histone deacetylases (HDACs) which act as corepressors, together with other corepressor proteins that are subsequently recruited.

These fundamental mechanisms have now been applied to understanding the regulation of inflammatory genes in diseases such as asthma. In a human epithelial cell line, by exposing the cell to inflammatory signals such as IL-1β, tumor necrosis factor α (TNF-α), or endotoxin, activation of NF-κB results in acetylation of specific lysine residues on histone H4 (the other histones do not appear to be as markedly or rapidly acetylated), and this is correlated with increased expression of genes encoding inflammatory proteins, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) [5].

**Histone deacetylases and corepressors**

The acetylation of histone that is associated with increased expression of inflammatory genes is counteracted by the activity of HDACs, of which 11 that deacetylase histones are now characterized [6,7]. There is now evidence that the different HDACs target different patterns of acetylation [8]. In biopsies from patients who have asthma there is an increase in HAT and a reduction in HDAC activity, thereby favoring increased inflammatory gene expression [9]. With this background it is now possible to understand better why corticosteroids are so effective in suppressing this complex inflammatory process that involves the increased expression of multiple inflammatory proteins. HDACs act as corepressors in consort with other corepressor proteins, such as nuclear receptor corepressor (NCoR) and silencing mediator of retinoic acid and thyroid hormone receptor (SMRT), forming a corepressor complex that silences gene expression [10].

**Cellular effects of corticosteroids**

Corticosteroids are the only therapy that effectively suppresses the inflammation in asthmatic airways, and this underlies the clinical improvement in
Asthma symptoms and prevention of exacerbations. At a cellular level, corticosteroids reduce the numbers of inflammatory cells in the airways, including eosinophils, T lymphocytes, mast cells, and dendritic cells (Fig. 1). These remarkable effects of corticosteroids are produced through inhibiting the recruitment of inflammatory cells into the airway by suppressing the production of chemotactic mediators and adhesion molecules and by inhibiting the survival in the airways of inflammatory cells, such as eosinophils, T lymphocytes, and mast cells. Epithelial cells may be a major cellular target for inhaled corticosteroids. Thus, corticosteroids have a broad spectrum of anti-inflammatory effects in asthma, with inhibition of multiple inflammatory mediators and inflammatory and structural cells. It is probably the broad anti-inflammatory profile of corticosteroids that accounts for their marked clinical effectiveness in asthma. Attempts to find alternative treatments that are more specific, such as inhibitors of single mediators, have usually been unsuccessful, emphasizing the importance of simultaneously inhibiting many inflammatory targets. Any explanation of the anti-inflammatory effects of corticosteroids needs to account for this broad spectrum of anti-inflammatory effects.

**Glucocorticoid receptors**

Corticosteroids diffuse readily across cell membranes and bind to glucocorticoid receptors (GRs) in the cytoplasm. Cytoplasmic GRs are normally bound to proteins known as molecular chaperones, such as heat shock protein-90 (hsp90) and FK-binding protein, that protect the receptor and prevent its nuclear localization by covering the sites on the receptor that are needed for transport across the nuclear membrane into the nucleus [11]. There is a single gene
encoding human GRs, but several variants are now recognized as a result of transcript alternative splicing and alternative translation initiation [12]. GRα binds corticosteroids, whereas GRβ is an alternatively spliced form that binds to DNA but cannot be activated by corticosteroids. GRβ has a low level of expression compared with GRα. The GRβ isoform has been implicated in steroid-resistance in asthma, although whether GRβ can have any functional significance has been questioned in view of the low levels of expression compared with GRα.

GRs may also be modified by phosphorylation and other changes, which may alter the response to corticosteroids by affecting ligand binding, translocation to the nucleus, trans-activating efficacy, protein-protein interactions, or recruitment of cofactors [13]. For example, there are a number of serine/threonines in the N-terminal domain where GRs may be phosphorylated by various kinases.

Once corticosteroids have bound to GRs, changes in the receptor structure result in dissociation of molecular chaperone proteins, thereby exposing nuclear localization signals on GR. This exposure results in rapid transport of the

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**Fig. 2.** Corticosteroids may regulate gene expression in several ways. Corticosteroids enter the cell to bind to GRs in the cytoplasm that translocate to the nucleus. GR homodimers bind to GREs in the promoter region of steroid-sensitive genes, which may encode anti-inflammatory proteins. Less commonly, GR homodimers interact with negative GREs to suppress genes, particularly those linked to adverse effects of corticosteroids. Nuclear GRs also interact with coactivator molecules, such as CBP, which is activated by proinflammatory transcription factors, such as NF-κB, thus switching off the inflammatory genes that are activated by these transcription factors. SLPI, secretory leukoprotease inhibitor; MKP-1, mitogen-activated kinase phosphatase-1; IκB-α, inhibitor of NF-κB; GILZ, glucocorticoid-induced leucine zipper protein; POMC, proopiomelanocortin; CRF, corticotrophin releasing factor.
activated GR-corticosteroid complex into the nucleus, where it binds to DNA at specific sequences in the promoter region of corticosteroid-responsive genes known as glucocorticoid response elements (GREs). Two GR molecules bind together as a homodimer and bind to GRE, leading to changes in gene transcription. Interaction of GRs with GRE classically leads to an increase in gene transcription (trans-activation), but negative GRE sites have also been described where binding of GRs leads to gene suppression (cis-repression) (Fig. 2) [14]. There are few well-documented examples of negative GREs, but some are relevant to corticosteroid adverse effects, including genes that regulate the hypothalamic-pituitary axis (proopiomelanocortin and corticotrophin releasing factor), bone metabolism (osteocalcin), and skin structure (keratins).

Corticosteroid-induced gene transcription

Corticosteroids produce their effect on responsive cells by activating GR to directly or indirectly regulate the transcription of target genes. Few genes per cell are directly regulated by corticosteroids, but many are indirectly regulated through an interaction with other transcription factors and coactivators. GR homodimers bind to GRE sites in the promoter region of corticosteroid-responsive genes. Interaction of the activated GR dimer with GRE usually increases transcription. GRs may increase transcription by interacting with coactivator molecules, such as CBP, thus activating histone acetylation and gene transcription. For example, high concentrations of corticosteroids increase the secretion of the antiprotease secretory leukoprotease inhibitor (SLPI) from epithelial cells [5].

The activation of genes by corticosteroids is associated with a selective acetylation of lysine residues 5 and 16 on histone H4, resulting in increased gene transcription (Fig. 3) [5]. Activated GRs may bind to coactivator molecules, such as CBP, steroid-receptor coactivator-1 (SRC-1), and glucocorticoid receptor interacting protein-1 (GRIP-1 or SRC-2), which all possess HAT activity [15].

Anti-inflammatory gene activation

Several of the genes that are switched on by corticosteroids have anti-inflammatory effects, including annexin-1 (lipocortin-1), SLPI, IL-10, and the inhibitor of NF-κB, IκB-α. However, therapeutic doses of inhaled corticosteroids have not been shown to increase annexin-1 concentrations in bronchoalveolar lavage fluid [16] and an increase in IκB-α has not been shown in most cell types, including epithelial cells [17]. Corticosteroids also switch on the synthesis of two proteins that affect inflammatory signal transduction pathways: glucocorticoid-induced leucine zipper protein (GILZ), which inhibits NF-κB and AP-1 [18], and mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1),
which inhibits p38 MAP kinase [19]. However, it seems unlikely that the widespread anti-inflammatory actions of corticosteroids could be entirely explained by increased transcription of small numbers of anti-inflammatory genes, particularly as high concentrations of corticosteroids are usually required for this effect, whereas in clinical practice corticosteroids are able to suppress inflammation at low concentrations.

**Adverse effect gene repression**

Little is known about the molecular mechanisms of corticosteroid adverse effects, such as osteoporosis, growth retardation in children, skin fragility, and metabolic effects. These actions of corticosteroids are related to their endocrine effects. The systemic adverse effects of corticosteroids may be caused by gene activation. Some insight into this has been provided by mutant GRs, which do not dimerize and therefore cannot bind to GRE to switch on genes. In transgenic mice expressing these mutant GR corticosteroids show no loss in their anti-inflammatory effects and are able to suppress NF-κB–activated genes in the normal way [20]. Several of the genes associated with adverse effects, including
the hypothalamo-pituitary axis, bone metabolism, and skin structure, appear to be regulated by interaction of GRs with negative GRE sites [14].

**Switching off inflammatory genes**

In controlling inflammation, the major effect of GCSs is to inhibit the synthesis of multiple inflammatory proteins through suppression of the genes that encode them, such as those shown in Box 1. Although this was originally believed to be through interaction of GR with negative GRE sites, these have been demonstrated on only a few genes, which do not include genes encoding inflammatory proteins [14].

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**Box 1. Effect of corticosteroids on gene transcription**

*Increased transcription (trans-activation)*

- Annexin-1 (lipocortin-1, phospholipase A$_2$ inhibitor)
- β$_2$-adrenergic receptor
- 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)
- GILZ
- MKP-1
- IL-10 (indirectly)

*Decreased transcription (trans-repression)*

- Cytokines: 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, and SCF
- Chemokines: IL-8, released by normal activated T cells expressed and secreted, macrophage inflammatory protein-1α, monocyte chemoattractant protein (MCP)-1, MCP-3, MCP-4, and eotaxins
- Adhesion molecules: intracellular adhesion molecule-1, vascular-endothelial cell adhesion molecule-1, and E-selectin
- Inflammatory enzymes: inducible nitric oxide synthase, inducible cyclooxygenase, and cytoplasmic phospholipase A$_2$
- Inflammatory receptors: tachykinin neurokinin (NK)$_1$-receptors, NK$_2$-receptors, and bradykinin B$_2$-receptors
- Peptides: endothelin-1
Interaction with transcription factors

Activated GRs have been shown to interact functionally with other activated transcription factors. Most of the inflammatory genes that are activated in asthma do not have GRE sites in their promoter regions, yet are potently repressed by GCSs. There is persuasive evidence that GCSs inhibit the effects of pro-inflammatory transcription factors, such as AP-1 and NF-κB, that regulate the expression of genes that code for many inflammatory proteins, such as cytokines, inflammatory enzymes, adhesion molecules, and inflammatory receptors [3]. Activated GRs can interact directly with other activated transcription factors by protein–protein binding, but this may be a particular feature of cells in which these genes are artificially overexpressed, rather than a property of normal cells. Treatment of patients who have asthma with high doses of inhaled GCSs that suppress airway inflammation is not associated with any reduction in NF-κB binding to DNA, yet is able to switch off inflammatory genes, such as GM-CSF, that are regulated by NF-κB [21]. This finding suggests that GCSs are more likely to be acting downstream of the binding of proinflammatory transcription factors to DNA, and attention has now focused on their effects on chromatin structure and histone acetylation.

Effects on histone acetylation

Activated GR may bind to CBP or other coactivators directly to inhibit their HAT activity [5], thus reversing the unwinding of DNA around core histones and thereby repressing inflammatory genes. More importantly, particularly at low concentrations that are likely to be relevant therapeutically in asthma treatment, activated GRs recruit histone deacetylase (HDAC)2 to the activated transcriptional complex, resulting in deacetylation of histones and thus a decrease in inflammatory gene transcription (Fig. 4) [5]. Using a chromatin immunoprecipitation assay, Ito and colleagues [5] demonstrated that corticosteroids recruit HDAC2 to the acetylated histone H4 associated with the GM-CSF promoter. In another study, using interference RNA to selectively suppress HDAC2 in an epithelial cell line, Ito and colleagues showed that there is an increase in the expression of GM-CSF and reduced sensitivity to corticosteroids [22]. By contrast, knock-down of HDAC1 and HDAC3 had no such effect on steroid responsiveness. An important issue that is not yet resolved is why corticosteroids selectively switch off inflammatory genes while having no effect on genes that regulate proliferation, metabolism, and survival. It is likely that GR only binds to coactivators that are activated by proinflammatory transcription factors, such as NF-κB and AP-1, although it is not yet understood how this specific recognition occurs.

Other histone modifications

Core histones may be modified not only by acetylation but also by methylation, phosphorylation, and ubiquitination and these modifications may
also regulate gene transcription [23]. Methylation of histones, particularly histone H3, by histone methyltransferases, usually results in gene suppression. The anti-inflammatory effects of corticosteroids are reduced by a methyltransferase inhibitor, 5-aza-2'-deoxycytidine, suggesting that this may be an additional mechanism whereby corticosteroids suppress genes [24]. Indeed there may be an interaction between acetylation, methylation, and phosphorylation of histones, so that the sequence of chromatin modifications (the so called “histone code”) may give specificity to expression of particular genes [25].

**Nontranscriptional effects**

Although most of the actions of GCSs are mediated by changes in transcription through chromatin remodelling, it is increasingly recognized that they may also affect protein synthesis by reducing the stability of mRNA so that less protein is synthesized. It is also increasingly recognized that several inflammatory proteins are regulated posttranscriptionally at the level of mRNA stability [26]. This regulation may be an important anti-inflammatory mechanism as it allows GCSs to switch off the ongoing production of inflammatory proteins after the inflammatory gene has been activated. The stability of some in-
flammatory genes is determined by regulation of adenine and uracil (AU)-rich elements (ARE) in the 3′-untranslated regions of the gene that interact with several ARE-binding proteins, such as human antigen R (HuR) and tristetraprolin, that may stabilize mRNA [27]. Some inflammatory genes, such as the genes encoding GM-CSF and cyclooxygenase-2 (COX2), produce mRNA that is particularly susceptible the action of ribonucleases that break down mRNA, thus switching off protein synthesis. GCSs may have inhibitory effects on the proteins that stabilize mRNA, leading to more rapid breakdown and thus a reduction in inflammatory protein expression [28,29]. GCSs do not appear to have any effect on HuR or tristetraprolin expression, however [30].

Effects on signal transduction pathways

GCSs have complex effects of signal transduction pathways through trans-repression of critical enzymes involved in inflammatory cascades or through increased transcription of endogenous inhibitors of these pathways.

Mitogen-activated protein kinase pathways

Mitogen-activated protein (MAP) kinases play an important role in inflammatory gene expression through the regulation of proinflammatory transcription factors. There is increasing evidence that GCSs may exert an inhibitory effect on these pathways. GCSs may inhibit AP-1 and NF-κB through an inhibitory effect on c-Jun N-terminal kinases (JNK), which activate these transcription factors [31]. GCSs reduce the stability of mRNA for some inflammatory genes, such as COX2, through an inhibitory action on another MAP kinase, p38 MAP kinase [27]. p38 MAP kinase regulates multiple inflammatory genes, including TNF-α, IL-1β, IL-6, GM-CSF, and IL-8, which have ARE sites in their 3′ untranslated regions, by stabilizing their mRNA so that synthesis is of the inflammatory protein is increased [27]. The inhibitory effect of GCSs is mediated through the rapid induction of a potent endogenous inhibitor of p38 MAP kinase, MKP-1, which is one of the genes switched on by GCSs (Fig. 5) [32]. GCSs not only induce the MKP-1 gene but also reduce its degradation. MKP-1 inhibits all MAP kinase pathways and therefore inhibits JNK and, to a lesser extent, extracellularly regulated kinase (ERK), in addition to p38 MAP kinase [32]. This activity indicates that GCSs have the capacity to inhibit all MAP kinase pathways, but the selectivity of MKP-1 for different MAP kinases seems to vary from cell to cell [33].

Steroid resistance

Although GCSs are highly effective in the control of asthma and other chronic inflammatory or immune diseases, a small proportion of patients who have
asthma fail to respond even to high doses of oral GCSs [34,35] and patients who have COPD are largely unresponsive to GCSs. Resistance to the therapeutic effects of GCSs is also recognized in nonpulmonary inflammatory and immune diseases, including rheumatoid arthritis and inflammatory bowel disease. Patients who are resistant to steroids present considerable management problems as there are few alternative anti-inflammatory treatments available. The new insights into the mechanisms whereby GCSs suppress chronic inflammation have shed light on the molecular basis for steroid resistance in asthma and COPD.

Steroid-resistant asthma

There may be several molecular mechanisms for resistance to the effects of GCSs and these may differ between patients [34,35]. It is likely that there is a spectrum of steroid responsiveness, with the rare resistance at one end, but a relative resistance is seen in patients who require high doses of inhaled and oral steroids (steroid-dependent asthma).
Biopsy studies have demonstrated the typical eosinophilic inflammation in the bronchial mucosa in these patients, with increased expression of Th2 cytokines. There is also resistance to the anti-inflammatory effects of GCSs in circulating mononuclear cells [36]. Certain cytokines (particularly IL-2, IL-4, and IL-13, which show increased expression in bronchial biopsies of patients who have steroid-resistant asthma) may induce a reduction in affinity of glucocorticoid receptors in inflammatory cells such as T lymphocytes, resulting in local resistance to the anti-inflammatory actions of GCSs. The combination of IL-2 and IL-4 induces steroid resistance in vitro through activation of p38 MAP kinase, which phosphorylates GRs and reduces GCS binding affinity within the nucleus [37]. The therapeutic implication is that p38 MAP kinase inhibitors now in clinical development might reverse this form of steroid resistance.

Another proposed mechanism for steroid resistance in asthma is increased expression of GR\(\beta\), which may theoretically act as an inhibitor by competing with GR\(\alpha\) for binding to GRE sites or from interacting with coactivator molecules [38]. However, there is no increased expression of GR\(\beta\) in the mononuclear cells of patients who have steroid-dependent asthma that have a reduced responsiveness to GCSs in vitro. Furthermore, GR\(\alpha\) greatly predominates over GR\(\beta\), making it unlikely that it could have any functional inhibitory effect [39], and GR\(\beta\) protein is undetectable in blood monocytes of patients who have asthma [40]. There is also no evidence for induction of GR\(\beta\) in response to IL-2/IL-4 exposure, which induces steroid-resistance in mononuclear cells, convincingly demonstrating that GR\(\beta\) cannot account for steroid resistance in asthma [40].

Another proposed mechanism is a failure of GRs to inhibit the activation of inflammatory genes by transcription factors such as NF-\(\kappa\)B and AP-1. There is defective inhibiting of AP-1 in response to GCSs in mononuclear cells of steroid-resistant patients [36]. This inhibition may be caused by increased activation of AP-1 caused by excessive activation of the JNK pathway, which has been demonstrated in the cells of steroid-resistant asthma patients [41].

Mononuclear cells from patients who have asthma and are steroid-dependent or -resistant show reduced suppression of cytokine release and a reduction in histone H4 acetylation in the nucleus following treatment with a high concentration of dexamethasone (1 \(\mu\)mol) [42]. In one group of patients, nuclear localization of GRs in response to a high concentration of GCSs is impaired, which accounts for the reduced histone acetylation as there is a direct correlation between the degree of histone acetylation and the GR nuclear localization [42]. This finding may be a result of GR nitrosylation, leading to reduced dissociation of GR from hsp-90 [43]. However, in another group of patients the defect in
acetylation of histone acetylation is found despite normal nuclear localization of GR. This finding may be a result of GR phosphorylation within the nucleus caused by the activation of p38 MAP kinase [37], which may result in a failure to recruit a distinct coactivator. This finding may result in failure of GRs to \textit{trans}-activate steroid-responsive genes [44]. In this group of patients, specific acetylation of histone H4 lysine-5 by GCSs is defective [42]. This defective acetylation presumably means that GCSs are not able to activate certain genes that are critical to the anti-inflammatory action of high doses of GCSs, but whether this is a rare genetic defect is not yet known.

\textit{Smoking asthmatics}

Patients who have asthma and smoke have more severe disease and are also resistant to the anti-inflammatory effects of GCSs [45]. A plausible explanation for this steroid resistance is the combined effect of asthma and cigarette smoking on HDAC, resulting in a marked reduction comparable to that seen in patients who have COPD, which is confirmed by the preliminary data in the study by Murahidy and colleagues [46].

\textit{Steroid resistance in chronic obstructive pulmonary disease}

Although inhaled GCSs are highly effective in asthma, they provide little therapeutic benefit in COPD despite the fact that active airway and lung inflammation is present. This fact may reflect that the inflammation in COPD is not suppressed by GCSs, with no reduction in inflammatory cells, cytokines, or proteases in induced sputum even with oral GCSs. Furthermore, histologic analysis of peripheral airways of patients who have severe COPD shows an intense inflammatory response, despite treatment with high doses of inhaled GCSs [47]. There is increasing evidence for an active steroid resistance mechanism in COPD, as corticosteroids fail to inhibit cytokines (such as IL-8 and TNF-\(\alpha\)) that they normally suppress [48,49]. In vitro studies show that cytokine release from alveolar macrophages is markedly resistant to the anti-inflammatory effects of GCSs compared with cells from normal smokers, and these alveolar macrophages are more resistant than alveolar macrophages from nonsmokers [50]. This lack of response to GCSs may be explained, at least in part, by an inhibitory effect of cigarette smoking and oxidative stress on HDAC function, thus interfering with the critical anti-inflammatory action of GCSs [51]. There is a correlation between HDAC activity and the suppressive effects of GCSs on cytokine release. It is likely that oxidative and nitrative stress in COPD specifically impair HDAC2 [52], resulting in steroid resistance (Fig. 6) [53]. Although these stresses are seen in all stages of COPD, they are most marked in the patients who have the most severe disease [54]. Even in patients who have COPD and have stopped smoking, the steroid resistance persists, and these patients are known to have continuing oxidative stress.
Oxidative stress is also increased in patients who have severe asthma and during exacerbations [55], so that a reduction in HDAC may also account for the reduced responsiveness to GCSs in these patients and the relative unresponsiveness of acute exacerbation of asthma to GCSs.

Summary

GCSs exert their anti-inflammatory effects through influencing multiple signal transduction pathways. Their most important action is switching off multiple activated inflammatory genes through inhibition of HAT and recruitment of HDAC2 activity to the inflammatory gene transcriptional complex. In addition, GCSs may activate several anti-inflammatory genes and increase the degradation of mRNA encoding certain inflammatory proteins. This broad array of actions may account for the striking effectiveness of GCSs in complex inflammatory diseases such as asthma and the difficulty in finding alternative anti-inflammatory drugs. There is now a better understanding of how the responsiveness to GCSs is
reduced in patients who have severe asthma, who have asthma and smoke, and who have COPD. An important mechanism now emerging is a reduction in HDAC2 activity as a result of oxidative stress. These new insights into GCS action may lead to new approaches to treating inflammatory lung diseases and in particular to increasing effectiveness of steroids in situations where they are less effective.

References


