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32.1 Introduction

CORTISOL secretion by the cortex of the adrenal glands (Fig. 32.1) increases in response to any stress in the body, whether physical (such as illness, trauma, surgery or temperature extremes) or psychological. However, this hormone is more than a simple marker of stress levels—it is necessary for the correct functioning of almost every part of the body. Excesses or deficiencies of this crucial hormone also lead to various physical symptoms and disease states [1]. Although cortisol is not essential for life per se, it helps an organism to cope more efficiently with its environment with particular metabolic actions on glucose production and protein and fat catabolism. Nevertheless, loss or profound diminishment of

cortisol secretion leads to a state of abnormal metabolism and an inability to deal with stressors, which, if untreated, may be fatal [1, 2].

The body's level of cortisol in the bloodstream displays a DIURNAL VARIATION, that is, normal concentrations of cortisol vary throughout a 24-h period (Fig. 32.1). Cortisol levels in normal individuals are highest in the early morning at around 8 a.m. and are lowest just after midnight. This early morning dip in cortisol level often corresponds to increased symptoms of inflammatory diseases or other pathologies in man [3]. Overlaid upon this diurnal variation is the pulsatile nature of cortisol release under the control of local and central 'clocks' [4]. By mimicking this pulsatile cortisol release, it is hoped to reduce the detrimental side effects of exogenous corticosteroids

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Fig. 32.1 The secretion of cortisol by the adrenal cortex is under the control of many feedback loops. In response to many external and internal stimuli (such as circadian rhythm and stress responses), neurons in the paraventricular nucleus of the hypothalamus release the corticotropin-releasing hormone (CRH) that travels to the anterior pituitary, where it stimulates the corticotroph cells of the anterior pituitary to release the adrenocorticotrophic hormone (ACTH) that by binding to cell surface ACTH

receptors, located primarily on the adrenocortical cells of the adrenal gland, stimulates the production of both glucocorticoids (cortisol) and mineralocorticoids (aldosterone), which are termed for this reason corticosteroids. Cortisol has many functions in different cells and tissues, including hepatic gluconeogenesis (for this reason the molecules mimicking its effect are also termed glucocorticoids). Cortisol also inhibits the secretion of both CRH and ACTH

whilst enhancing their anti-inflammatory properties [4, 5].

Increased levels of corticosteroids serve as potent suppressors of the IMMUNE AND INFLAMMATORY SYSTEMS. This is particularly evident when they are administered at pharmacological doses but is also important in controlling normal immune responses. As a consequence, corticosteroids are widely used as drugs to treat many different inflammatory and autoimmune diseases such as rheumatic diseases [e.g., rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)], inflammatory diseases of the upper airways (rhinitis, chronic rhinosinusitis), pulmonary inflammatory diseases [bronchial asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung diseases (such as sarcoidosis, hypersensitivity pneumonias, idiopathic eosinophilic pneumonias,

idiopathic fibrosing interstitial pneumonias)], inflammatory bowel disease (IBD, Crohn's disease and ulcerative colitis), infections (including tuberculosis), inflammatory skin diseases (e.g., psoriasis, atopic dermatitis) and kidney diseases (e.g., glomerulonephritis). Corticosteroids may also be used in organ transplantation to reduce the chance of rejection (see Chap. 32). Thus, although the early effect of cortisol is to stimulate the immune system, cortisol and synthetic corticosteroids predominantly repress the inflammatory response by decreasing the activity and production of immunomodulatory and inflammatory cells.

The usefulness of corticosteroids in treating inflammatory diseases was exemplified by the early work of Kendall and Hench [6]. In a classic experiment, 100 mg of cortisone was injected into the muscle of a patient (Mrs. G.) suffering

from chronic rheumatoid arthritis on Sept 21, 1948. Seven days later the patient was able to walk to the shops for the first time in years. Kendall and Hench were awarded the Nobel prize for this work in 1950, and it represented a new approach to therapy with natural hormones by utilising pharmacological, rather than physiological, doses.

There are five main aspects of inflammation: (1) the release of inflammatory mediators such as histamine, lipid mediators, complement factors, CYTOKINES AND CHEMOKINES, other growth factors and neuropeptides and gaseous mediators; (2) increased blood flow in the inflamed area (erythema) caused by some of these inflammatory mediators; (3) leakage of plasma from the vasculature into the damaged area (oedema) due to increased capillary permeability; (4) cellular infiltration signalled by chemoattractants; and (5) repair processes such as tissue fibrosis. Corticosteroids can modify all of these processes.

Inflammation is a central feature of many chronic diseases (please see above). The specific characteristics of the INFLAMMATORY SYSTEM and the inflammatory response in each disease and the site of inflammation differ, but both involve the recruitment and activation of inflammatory cells and changes in the structural cells of the target organ. All are characterised by an increased expression of many INFLAMMATORY MEDIATORS including cytokines, chemokines, growth factors, enzymes, receptors and ADHESION MOLECULES. The increased expression of these proteins is the result of enhanced gene transcription since many of the genes are not expressed in normal cells but are induced in a cell-specific manner during the inflammatory process [7].

32.2 Chemical Structures

Corticosteroids are 21-carbon steroid hormones (Fig. 32.2) composed of four rings [8, 9]. The basic structure of the A ring is a 1 α , 2 β -half-chair, whatever the substitutions. Rings B and C are semi-rigid chairs with minimal structural

influence by substituent groups. In contrast, the shape of the D-ring depends on the nature and environment of the substituent groups. Modern corticosteroids such as prednisone, prednisolone, fluticasone, budesonide, dexamethasone and deflazacort are based on the cortisol (hydrocortisone) structure with modification to enhance the anti-inflammatory effects such as insertion of a C=C double bond at C1,C2 or by the introduction of 6 α -fluoro, 6 α -methyl and 9 α -fluoro and/or further substitutions with α -hydroxyl, α -methyl or β -methyl at the 16 position, for example, in dexamethasone (Fig. 32.2) [8, 9]. Reduced binding to the mineralocorticoid receptor is achieved by insertion of the C=C double bond at C1,C2, and lipophilic substituents such as 21 α -esters attached to the D-ring increase glucocorticoid receptor (nuclear receptor subfamily 3, group C, member 1; NR3C1; GR) binding and enhance topical deposition and hepatic metabolism. These substitutions are seen with budesonide and fluticasone two of the most commonly used inhaled corticosteroids [8, 9]. Beclomethasone dipropionate (BDP) is a prodrug of the active form, beclomethasone (beclomethasone-17-monopropionate, BMP). Ciclesonide is a prodrug that is enzymatically hydrolysed, by esterase enzymes of the airways, to a pharmacologically active metabolite, C21-desisobutyl-ciclesonide (also termed des-ciclesonide or RM1). The ligand-binding domain (LBD) of GR has a pocket on the floor of the binding cleft that lies beneath the C17 residue of the steroid backbone. The degree of occupancy of this pocket affects the affinity, duration of action and side effect profile of ligands, and computational chemistry can design drugs with improved clinical characteristics including those without a steroid backbone to improve safety [10].

Using this structural knowledge has allowed the production of non-steroidal GR agonists (SEGRAs) or selective glucocorticoid receptor modulators (SEGRMs) which fill the GR ligand-binding domain spatially and have many classical GR activities but can avoid the side effects associated with the steroid backbone such as association with other steroid receptors [11]. The latter class is able to modulate the activity of a GR agonist and/or may not classically bind

Fig. 32.2 Structural modifications of cortisol exhibited by the clinically used corticosteroids prednisone, prednisolone, deflazacort, dexamethasone and triamcinolone, beclomethasone dipropionate, budesonide, ciclesonide,

fluticasone (propionate and furoate) and mometasone. Most of the images have been obtained from https://commons.wikimedia.org/wiki/Main_Page

the GR LBD. SEGRMs were expected to present the same or better efficacy compared to classical corticosteroids but cause minimal side effects. SEGRAs and SEGRMs are collectively denominated SEGRAMs (selective glucocorticoid receptor agonists and modulators) [11]. Although this transrepression vs transactivation concept has been proved to be too simplistic, the SEGRAMs have been helpful in elucidating various molecular actions of the glucocorticoid receptor [11]. The exact structural and lipophilic requirements to optimise corticosteroid pharmacokinetics and pharmacodynamics to separate their anti-inflammatory efficacy from their side effects are still unclear, but corticosteroids with improved clinical characteristics are likely to be synthesised as our knowledge in this area increases.

32.3 Mechanisms of Corticosteroid Action

32.3.1 Glucocorticoid Receptors

Classically, corticosteroids exert their effects by binding to a single receptor but with many isoforms. The glucocorticoid receptors [GRs or nuclear receptor subfamily 3 group C member 1 (NR3C1)] are transcription factors belonging to the superfamily of nuclear receptors that are localised to the cytoplasm of target cells. GRs are expressed in almost all cell types, and their density varies from 200 to 30,000 per cell [9, 12] with an affinity for cortisol of ~30 nM, which falls within the normal range for plasma concentrations of free hormone. The human GR gene is located on the long arm of the chromosome 5 and

expresses two major mRNAs variants, termed GR α (previously GR α) and GR β (GR β). The human GR α mRNA further expresses multiple isoforms [named GR α -A (classic form), GR α -B, GR α -C1, GR α -C2, GR α -C3, GR α -D1, GR α -D2 and GR α -D3]. All human GR α isoforms translocate into the nucleus in response to ligand, while they are differentially distributed in the cytoplasm and/or the nucleus in the absence of ligand. GR α -B and GR α -C1 possess transcriptional activities similar to that of GR α -A, whereas GR α -C2 and GR α -C3 isoforms have stronger transcriptional activities, while GR α -D1, GR α -D2 and GR α -D3 demonstrate weaker activities [9, 12–15].

GR exists in all cells within the airways as the predominant GR α -A isoform explaining the pronounced effect that corticosteroids have on airway resident and inflammatory cells and their clinical efficacy in most subjects with asthma [9, 12–15].

The GR β isoform has been implicated in corticosteroid insensitivity in some patients by acting as a dominant negative regulator of GR α -A [9, 12–16].

The GR has several functional domains (Fig. 32.3). The corticosteroid ligand-binding domain (LBD) is sited at the carboxyl terminus of the molecule and is separated from the DNA binding domain (DBD) by a hinge region. There is an N-terminal transactivation domain which is involved in gene activation following DNA binding. This region may also be involved in binding to other transcription factors. The inactive GR is part of a large protein complex (~300 kDa) that includes two subunits of the heat shock protein hsp90, which blocks the nuclear localisation of GR and one molecule of the immunophilin p59, termed FK506-binding protein 2 (FKBP2 also known as PPIase or FKBP-13), based on its ability to bind the immunosuppressive drug FK506 [9, 12].

Corticosteroids are lipophilic and diffuse freely from the circulation into cells across the cell membrane and bind the ligand-binding domain of their GR to induce activation (Fig. 32.4) [9, 12–15]. Once activated, GR translocates into the nucleus where it interacts with transcriptional coactivators or repressors to modulate GENE TRANSCRIPTION repressing

inflammatory genes (TRANSREPRESSION) or enhancing the expression of anti-inflammatory genes (TRANSACTIVATION). This because once the corticosteroid binds to GR, hsp90 dissociates revealing nuclear localisation signals (NLS) allowing the nuclear translocation of the activated GR-corticosteroid complex and its binding to DNA.

Shuttling of GR between the nucleus and cytoplasm is regulated by nuclear import and export receptors in a dynamic manner. GR possess two NLS, NLS1 and NLS2. GR interacts with several importins including importins 7, 8 and 13 and the α/β heterodimer. Defects in nuclear translocation observed in patients with relative steroid-resistant severe bronchial asthma may result from abnormal levels of importin 7 or its ability to interact with GR under the influence of oxidative stress [9, 14, 17–20]. GR translocates into mitochondria and lysosomes as well [14].

The function of GR is affected by many post-translational modifications, particularly phosphorylation, acetylation, sumoylation and nitration, and these can have major effects on all aspects of GR function, from ligand binding and nuclear translocation to cofactor association and control of gene transcription with the effect of phosphorylation being the most studied. Correct GR phosphorylation is essential for optimal GR function with phosphorylation at both Ser226 and Ser221 being seen with GR activation. Ser211 phosphorylation has been linked to alterations in ligand binding, nuclear translocation and transactivation and cofactor association. GR Ser226 phosphorylation, in contrast, is associated with greater transcription efficacy [9, 12, 14, 15, 20–22].

GR can also be acetylated on lysines K494 and K495 following activation. Acetylation of GR affects the ability of GR to interact with p65 (see below), and removal of these tags is important for the suppression of subsets of inflammatory genes [9, 12, 14, 15, 23]. Small ubiquitin-like modifier (SUMO) proteins can also modify GR and affect its function. Sumoylation affects GR transactivation potential particularly at promoters with multiple GREs, whilst K293 GR

Fig. 32.3 Modular structure of the glucocorticoid receptor (GR). The coding region of GR results from splicing together of exons 2–9 of the GR gene. The GRβ isoform of GR results from the use of the short 9β exon which removes the ligand-binding domain seen in GRα. The modular design of GR enables distinct regions of the protein to function in isolation as ligand-binding domains, dimerisation domains, nuclear localisation domains, transactivation and transrepression (AP-1 and NF-κB interacting) domains. *NLS* nuclear localisation signal, *AF-1/2* activating factor 1/2, *GRE* glucocorticoid response element (composed of two palindromic half sites (AGAACAA) separated by three nucleotides)

Fig. 32.4 Mechanisms of gene repression by the glucocorticoid receptor (GR). The glucocorticoid can freely migrate across the plasma membrane where it associates with the cytoplasmic GR. This results in activation of the GR and dissociation from the heat shock protein (hsp90) chaperone complex. Firstly, activated GR translocates to the nucleus where it can bind as a monomer either directly or indirectly with the transcription factors, activator protein-1 (AP-1) and nuclear factor kappa B (NF-κB), preventing their ability to switch on inflammatory gene

expression ①. Secondly, the GR dimer can bind to a glucocorticoid response element (GRE) that overlaps the DNA binding site for a pro-inflammatory transcription factor or the start site of transcription thereby preventing inflammatory gene expression ②. Thirdly, the GR dimer can induce the expression of the NF-κB inhibitor IκBα ③, and fourthly glucocorticoids can increase the levels of cell ribonucleases and mRNA destabilising proteins, thereby reducing the levels of mRNA ④

SUMOylation is essential for GC-induced inverted repeated negative GC response element (IR nGRE)-mediated direct transrepression and for NF-κB/AP1-mediated GC-induced tethered indirect transrepression. In addition, cells with sumoylation-deficient FK506-binding protein 51 (FKBP51) fail to interact with Hsp90 and GR, thus facilitating the recruitment of the closely related protein, FKBP52, which enhances GR transcriptional activity [9, 24–26]. Finally, nitration of the GR results in an enhancement of GR-mediated transcriptional activity.

Nuclear GR can induce or repress gene expression following DNA binding at specific glucocorticoid response elements (GREs) or acting as a monomer interact with DNA-bound pro-inflammatory factors and thereby enable transcriptional regulator proteins to be positioned such that they repress activated gene expression. Pro-inflammatory transcription factors such as ACTIVATOR PROTEIN-1 (AP-1) and NUCLEAR FACTOR KAPPA B (NF-κB), which are upregulated during inflammation, are the major targets for this tethering process

although tethering between GR and p65 (the major subunit of NF-κB), for example, is not essential for repression in airway epithelial cells [9, 20, 27, 28].

It is likely that the altered transcription of many different genes is involved in the anti-inflammatory action of corticosteroids, but the most important action of these drugs is likely to be inhibition of transcription of cytokine and chemokine genes implicated in inflammation. Evidence for this has been presented in a series of elegant experiments using mice expressing mutated GRs unable to dimerise and subsequently bind to DNA [9, 15, 20].

32.3.2 Gene Induction by Corticosteroids

The GRE is the imperfect palindrome AGAACA_{nnn}TGTTCT with GR able to interact with each hexamer independently. Even small changes in the GRE sequence can have a profound effect on transcriptional activity. Indeed,

the GRE may be considered as a different type of GR ligand which is able to modify GR function by altering the association with transcriptional cofactors, changing the local chromatin configuration and thereby affecting downstream functional actions of GR [9, 28–30].

The activated GR only remains associated with the GRE for a few seconds before being replaced by a different GR in a process called assisted loading. Binding of the first GR to a GRE initiates an ATP-dependent chromatin remodelling process that provides site more amenable for GR-GRE interaction highlighting the importance of co-ordinated GRE interactions to obtain the full glucocorticoid (GC) response in a cell- and tissue-dependent manner [9, 31]. Combining DNase I accessibility assays with chromatin immunoprecipitation and high-throughput sequencing, the transcription factor activator protein 1 (AP-1) was identified as a major partner for productive GR-chromatin interactions. This highlighted the critical role for AP-1 in regulating GR-mediated transcription and recruitment to co-regulatory elements. Indeed, the baseline chromatin accessibility of GR recruitment to GREs is dependent on AP-1 binding. This may account for the importance of AP-1 and its components such as c-Jun in gene regulatory networks that distinguish asthmatic subjects who respond poorly to corticosteroids [32].

In airway epithelial cells, there are >10,000 GR binding sites (GBS), of which only 13% are able to induce transcriptional activation in response to GC exposure. The GBS lacking activation potential clustered around the inducible GBS, and interactions between these direct and tethered GBS are necessary for the full gene activation response to GC [9, 33].

Several genes are upregulated by glucocorticoids, including the β_2 adrenergic receptor (β_2 -AR), MAPK phosphatase (MKP-1/DUSP1) and serum leukoprotease inhibitor (SLPI). Interestingly, corticosteroids can also induce the expression of the NF- κ B inhibitor I κ B α in certain cell types.

Several other mechanisms of GR function have been reported including effects on mRNA

stability (Fig. 32.4). GCs affect the expression of pro-inflammatory gene mRNAs which contain adenylate-uridylate-rich elements (AREs) within their 3' untranslated regions through targeting the RNA-binding proteins tristetraprolin (TTP) and Hu antigen R (HuR) family members which control mRNA decay and stability, respectively. This mechanism is used by dexamethasone, for example, to downregulate COX-2 and CCL11 expression acting via the p38 MAPK-MKP-1 axis [9].

Also non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), modify GR expression and function. The expression of certain key miRNAs is regulated by GR, and GR is itself the target of other miRNAs. Induction of GILZ expression by GR is reduced by miR18 and miR124a in human cells, and aberrant expression of these miRNAs may be involved in the relative corticosteroid insensitivity in some patients with severe asthma. Hydrocortisone increases miR124 expression in sepsis patients which causes GRa downregulation and corticosteroid insensitivity [9]. Furthermore, inhibition of miR145 prevents eosinophilia, mucous secretion and airway hyper-responsiveness to the same extent as dexamethasone in an animal model of asthma.

Long ncRNAs (lncRNAs) are defined as being >200 nucleotides in length, and two specific lncRNAs have opposite effects on GR function. Steroid receptor RNA activator (SRA) is a constituent of the steroid receptor coactivator (SRC)-1/SRC-2 complex, and it increases GR transcriptional. In contrast, growth arrest-specific 5 (Gas5) is a GRE decoy by binding to the DNA binding site of active GR [9].

32.3.3 Gene Repression by Corticosteroids

GR plays a critical role in suppressing inflammatory gene expression. The mechanisms involved generally evoke tethering of activated GR to an activated transcriptional complex driven by DNA-bound NF- κ B, for example. The interaction between GR and NF- κ B is mutually antagonistic with GR repression seen with NF- κ B activation. Importantly, increased NF- κ B

activation at the nuclear localisation and expression level is associated with severe asthma.

This process is driven in part by HISTONE DEACETYLASE (HDAC)2-mediated alterations in GR acetylation status. HDAC2 expression and/or activity linked to enhanced HAT activity is reduced in severe asthma patients, particularly children. Interestingly, GR β has been reported to reduce HDAC2 expression in human BAL macrophages. A lack of HDAC activity may also evoke local changes in histone acetylation at inflammatory gene promoters, thereby modulating gene expression [9, 13, 15, 23, 30, 34–36]. Alterations in the phosphorylation status of RNA polymerase 2 C-terminal domain (CTD) have also been implicated in the mechanism of dexamethasone-induced suppression of TNF- α /NF- κ B-induced CXCL8 activation by preventing phosphorylated CTD from interacting with the basal transcription factor P-TEFb. A reduction in HDAC2 expression results in a failure to remove the CTD phosphorylation tag and stalling of RNA polymerase 2 on the promoters of steroid-responsive genes.

In addition to interactions with AP-1 and NF- κ B, GR can also associate with, and repress, the function of many other transcription factors including the signal transducer and activator of transcription (STAT) family of transcription factors. Many inflammatory (including some of the acute-phase response) genes are under STAT regulation induced by mediators such as interferons (IFNs), interleukin (IL)-5 and IL-6, for example. Interestingly, inflammatory mediators induced by IFN γ -stimulated airway epithelial cells can be inhibited by JAK-STAT inhibitors but not by corticosteroids [9, 37–39].

32.3.4 Non-genomic Rapid Actions of Corticosteroids

The traditional genomic theory of steroid action, whether through direct interaction with DNA or involving cross-talk with other transcription factors, does not fully explain the rapid effects of hormonal steroids, and it is thought that the non-genomic actions are mediated by a distinct

membrane receptor [40]. These receptors have distinctive hormone-binding properties, compared to the well-characterised cytoplasmic receptor, and are probably linked to a number of intracellular signalling pathways, acting through G-protein coupled receptors and a number of kinase pathways [40]. In addition, the classical receptor is associated with a variety of kinases and phosphatases within the inactive GR/hsp90 complex. These enzymes are released upon hormone binding and may also account for the rapid induction of tyrosine kinase activity seen in some cell types by glucocorticoids [41]. Evidence of immediate responses is also seen clinically since systemic doses of corticosteroid can lead to very rapid clinical improvement and inhibition of allergic/anaphylactic responses [42].

32.4 Pharmacological Effects of Corticosteroids

32.4.1 Effects of Corticosteroids on Inflammatory and Structural Cells

Corticosteroids are the only therapeutic agents that clearly reverse the inflammation present in many chronic inflammatory diseases of different organs and causes (see above) (see also Chaps. 23, 31 and 33). Topical and systemic corticosteroids have similar pharmacological effects, with differences related to the dose delivered to the target organ and to the enhanced effect of systemic corticosteroids on the mobilisation and recruitment of inflammatory cells from the blood and bone marrow.

In general, in all chronic inflammatory and immune diseases, corticosteroids cause a marked reduction in the number and activation of infiltrating cells, including mast cells, macrophages, T lymphocytes and eosinophils, in the inflamed tissue [9, 15]. Furthermore, topical and oral corticosteroids can have effects on structural cells and in asthma, for example, can reverse the bronchial epithelial damage, mucus hyperplasia and basement-membrane thickening that is

characteristically seen in the bronchial biopsies from these patients [9, 15].

Corticosteroids may have direct inhibitory effects on many of the cells involved in inflammation, including macrophages, T and B lymphocytes, eosinophils, smooth muscle and endothelial and epithelial cells, resulting in their reduced inflammatory mediator synthesis and release [9, 15, 43–45] (Fig. 32.5). In general, corticosteroids substantially reduce mast cell-/eosinophil-/lymphocyte-driven processes while leaving unaltered, or even augmenting, neutrophil-mediated processes [9, 15, 43–45]. For example, corticosteroids may enhance neutrophil function as a result of increased leukotriene B₄ and superoxide anion production, in addition to inhibiting their apoptosis [44]. GCs modulate inflammatory cell survival, inducing apoptosis in T and B lymphocytes and eosinophils while delaying constitutive neutrophil apoptosis and promoting non-inflammatory phagocytosis of apoptotic cell targets, a process important for the successful resolution of

inflammation [45, 46]. Corticosteroids in autoimmune diseases decrease the cell and tissue damage mediated by T cells and autoantibodies and immunocomplexes. Interestingly in allergic diseases, corticosteroids reduce the number of mast cells within the inflamed tissue; however, they do not appear to inhibit mediator release from these cells [9, 15, 43, 44]. Treatment with topical corticosteroids also reduces the number of activated T lymphocytes (CD25+ and HLA-DR+) in bronchoalveolar lavage (BAL) fluid and peripheral blood from asthmatic patients [47].

Corticosteroids are particularly effective against eosinophilic inflammation, possibly as a result of decreasing eosinophil survival by stimulating apoptosis [46, 48]. In addition to their suppressive effects on inflammatory cells, corticosteroids may also decrease endothelial permeability and inhibit plasma exudation and/or leucocyte transendothelial migration in most tissues [9, 15]. Inflammation drives angiogenesis by direct and indirect mechanisms, promoting endothelial proliferation, migration and vessel

Fig. 32.5 Glucocorticoids act on most inflammatory and structural cells of the tissues to suppress inflammation. The activity (T and B lymphocytes and macrophages) and number of infiltrating inflammatory cells (eosinophils, T and B lymphocytes, macrophages, mast cells and dendritic cells) are decreased by glucocorticoids.

Glucocorticoids also have a suppressive effect on structural cells of the tissues and can reduce inflammatory mediator release and adhesion molecule expression on epithelial and endothelial cells, microvascular leakage from blood vessels, angiogenesis and both the numbers of mucus cells and release of mucus from these cells

sprouting, but also by mediating extracellular matrix remodelling and release of sequestered growth factors and recruitment of proangiogenic leucocyte subsets. By facilitating greater infiltration of leucocytes and plasma proteins into inflamed tissues, angiogenesis can also propagate chronic inflammation [49], and high doses of topical systemic corticosteroids may reduce both neo-angiogenesis and the increased blood flow present at sites of inflammation [9, 15]. At sites of acute and/or chronic mucosal inflammation, there is often an increased secretion of the major secretory mucins (MUC5AC and MUC5B). The effect of the glucocorticoids on the expression of these mucins is still quite controversial and may be cell- and tissue-type dependent [50].

32.4.2 Effects of Corticosteroids on Inflammatory Mediator Production and/or Secretion and/or Activation

Corticosteroids block the generation of most pro-inflammatory cytokines and chemokines [9, 15, 51, 52]. Despite the wide pleiotropy (multiple actions) and redundancy that exists in the cytokine and chemokine families, and the subsequent inability to ascribe precise roles to most of these molecules in inflammatory disease pathogenesis, it is clear that these proteins are important mediators in chronic inflammation (see Chap. 5). The development of TUMOUR NECROSIS FACTOR- α (TNF- α) and INTERLEUKIN (IL)-1 β , IL-6, IL-12 and IL-23 antagonists has provided evidence that, in many inflammatory bowel, rheumatic and skin diseases, these mediators play a key driving role in inflammation, despite different clinical relevance of each inflammatory mediator in different tissues and diseases [53, 54] (see Chap. 33). This does not appear to be the case with all inflammatory diseases, however [9, 15, 51, 52]. Interestingly, corticosteroids can also enhance the expression of key anti-inflammatory molecules such as IL-10 and IL-1ra in some inflammatory diseases but again not all [9, 15]. For example, corticosteroids increase the production of IL-10, but not IL-1ra, at sites of inflammation in asthma [9, 15].

Arachidonic acid metabolism via 5-lipoxygenase gives rise to a group of biologically active lipids known as LEUKOTRIENES: leukotriene B₄, which is a potent activator of leucocyte chemotaxis, and cysteinyl leukotrienes (leukotriene C₄, D₄ and E₄) which account for the spasmogenic activity previously described as slow-reacting substance of anaphylaxis (see Chap. 7). Leukotrienes, particularly cysteinyl leukotrienes, are thought to play a key role in some chronic and acute inflammatory diseases but do not appear to be major targets for corticosteroids that are unable to block leukotriene biosynthesis and their release [55]. However, corticosteroids in vitro accelerate LTC₄ catabolism by inducing the activity of a LTC₄-degrading enzyme, gamma-glutamyl transpeptidase-related enzyme (γ -GTPRE) [56]. Analysis of serum from patients with increasing severity of asthma identified 15 metabolites that were significantly altered in asthma although some such as dehydroepiandrosterone sulphate, cortisone, cortisol, prolylhydroxyproline, pipercolate and N-palmitoyltaurine correlated significantly with ICS and oral corticosteroid use. In contrast, oleoylethanolamide increased with asthma severity independently of steroid treatment. Overall, the data indicated that asthma was characterised by a systemic metabolic shift according to disease severity and that corticosteroid treatment significantly affects metabolism [57].

32.4.3 Oxidative Stress and Reduced Response to the Corticosteroid Effects

The inflammation in COPD, in severe asthma and in a high number of patients with IBD is scarcely suppressed by topical or oral corticosteroids, even at very high doses. Potential reasons for the failure of corticosteroids to function effectively in reducing inflammation in these diseases include the fact that all of them have a high oxidative stress and oxidative stress may reduce corticosteroid receptor (GR) nuclear translocation with reduced GR α expression or altered GR-cofactor interactions within the nucleus [9, 15, 58, 59].

Interestingly, cigarette smoke contains 10^{17} oxidant particles per puff, and asthmatic subjects who smoke have a reduced responsiveness to both topical and oral corticosteroids [60–62].

32.4.4 Mechanisms of Reduced Corticosteroid Responsiveness in COPD

Oxidative stress reduces HDAC2 expression and activity, thus potentially limiting glucocorticoid effectiveness in suppressing inflammation in vitro studies and in patients with COPD. Overexpression of HDAC2, but not HDAC1, improves corticosteroid sensitivity in bronchoalveolar lavage (BAL) macrophages from stable COPD patients [23] through a mechanism that involves the phosphoinositide-3-kinase (PI3K)- δ pathway [9, 15]. Sub-bronchodilator low doses of theophylline, at concentrations that do not inhibit phosphodiesterase (PDE)4 activity, can enhance HDAC2 activity in vitro, and functionally this enhances glucocorticoid effects. Combined theophylline and ICS treatment improves lung function and sputum neutrophilia in stable COPD patients and lung function in smoking asthmatics [9, 15]. This effect may be via phosphoinositide-3-kinase (PI3K) δ -induced hyperphosphorylation of HDAC2 particularly since PI3K δ is upregulated in peripheral lung tissue of patients with COPD. Use of inhaled PI3K δ -selective inhibitors may even prove more efficacious in improving patient responses to ICS [63]. The results of an ongoing phase IIa large controlled study [<https://clinicaltrials.gov/ct2/show/NCT03345407>] on the efficacy of a highly selective inhaled PI3K δ inhibitor (GSK2269557) in patients with stable COPD are awaited with interest.

32.4.5 Mechanisms of Reduced Corticosteroid Responsiveness in Severe Bronchial Asthma

Some patients with severe asthma are unable to suppress asthmatic inflammation with high-dose ICS or even oral glucocorticoids. These patients

are distinct from those who are non-compliant with their treatment or subjects without access to the correct therapies. The reduced GC function in refractory asthma may be multifactorial, and each stage of GR activation, namely, GR expression, ligand binding, nuclear translocation and/or binding to the GRE and other transcription factors, has been proposed as a mechanism [9, 15, 64, 65].

It is possible that redox-sensitive activation of the AP pathway may drive relative steroid refractoriness in peripheral blood mononuclear cells (PBMCs) from severe steroid-refractory asthmatics [23]. Indeed, the expression of AP-1 components and its upstream activators is greater in PBMCs and bronchial biopsies from patients with corticosteroid-resistant asthma [35], and their expression is not altered by high doses of oral glucocorticoids [61]. In immortalised peripheral blood B cells, there is a distinct network connectivity and gene ontology pattern between good and poor corticosteroid responders which is linked to AP-1 components and a differential response to apoptosis [32].

Nitrosative stress may also impact upon corticosteroid responsiveness, and peroxynitrite formation causes nitration of specific tyrosine (Y) residues which results in the loss of enzymatic activity (Y146) and degradation (Y253) of HDAC2 [62]. However, reduced HDAC2 expression and/or activity is not seen in all patients with therapy-refractory asthma possibly reflecting the heterogeneity of severe asthma phenotype [64, 65].

The transcriptome of bronchial epithelial cells of mild/moderate asthmatics has identified a gene profile that predicts ICS responsiveness—namely, an IL-13-induced gene signature. The expression of this signature is variable in asthma and is inversely correlated with Th17 cells which are linked with steroid insensitivity and with IL-6 a marker of neutrophilic asthma which is also associated with more severe disease [9, 15, 64, 65].

In vitro high levels of IL-2, IL-4 and IL-13 reduce corticosteroid responses in T cells by reducing the affinity of GR for its ligand. This may reflect differences in GR phosphorylation status under the control of the p38 MAPK

pathway. Increased p38 MAPK activity is also seen in peripheral blood monocytes, and BAL macrophages from patients with severe asthma and p38 MAPK inhibitors restored GC responsiveness in these cells. Similar results are seen in cells from COPD patients. There is some evidence that this may be linked to changes in HDAC and HAT activities. p38 MAPK may also modulate GR responses by changing GR phosphorylation status. Phosphorylation of GR on Ser134 is p38 MAPK-dependent and significantly downregulates dexamethasone-dependent genome-wide transcriptional responses and cell functions. MKP-1/DUSP1 is a GC-inducible gene which dephosphorylates and inactivates p38 MAP kinases, and its expression and induction are impaired in severe asthma [9, 15, 64, 65].

The exact stimulus given to a cell modifies the intracellular pathway(s) activated, and other signalling pathways such as the MEK/ERK pathway have been implicated in controlling relative GC refractoriness. Furthermore, cyclin-dependent kinases (CDK), glycogen synthase kinase-3 and JNKs can also target GR phosphorylation or phosphorylation of GR-associated cofactors. Neutrophilic asthma is associated with GC refractoriness and increased IL-17 expression and Th17 cells. An animal model of asthma demonstrated that Th17 cell transfer causes a dexamethasone-insensitive neutrophilic inflammatory response and bronchial hyperresponsiveness to methacholine. More importantly, IL-17 inhibits budesonide sensitivity in primary human bronchial epithelial cells through modulating PI3K and HDAC2 expression [9, 15, 64, 65].

32.4.6 Mechanisms of Reduced Corticosteroid Responsiveness During Viral-Induced Asthmatic Exacerbations

Viral infections cause most of the asthmatic exacerbations in children and adults, and these exacerbations are not readily resolved by glucocorticoids, even when administered systemically at high doses. In human experimental models of virally induced asthmatic exacerbations,

neither ICS nor oral prednisolone prevents the worsening of airway inflammation or improves clinical symptoms. IFN γ may be one of the dominant mediators responsible for chronic persistent airflow obstruction in severe asthma, and primary bronchial epithelial cells stimulated with IFN γ do not respond to GC. These inflammatory responses are, however, completely ablated by treatment of cells with a JAK-STAT inhibitor. Exposure of primary human airway epithelial cells to RV-16 causes a relative GC resistance by preventing GR nuclear import. This is reversed by suppression of the RV-16-induced JNK and NF- κ B pathways [9, 15, 66].

32.5 Pharmacokinetics of Corticosteroids

The pharmacokinetics of many corticosteroids has been well described. In general, plasma concentrations of corticosteroids vary considerably (up to tenfold) after oral administration of the same dose by normal volunteers and asthmatic patients although the reasons for this are unclear [67]. The plasma half-life of currently used ICS varies from <2 h (budesonide) to >5 h [BDP/BMP, fluticasone (propionate and furoate) and mometasone]. This is in contrast to their biological effects which last for 18–36 h [10, 63, 68]. The pharmacokinetic properties of topical drugs depend upon a combination of tissue deposition/targeting, receptor binding, volume of distribution, tissue retention and lipid conjugation. In addition, in order to achieve a good therapeutic index, drugs need to possess a low oral bioavailability and small particle size, rapid metabolism, high clearance, high plasma protein binding and a low systemic half-life. Furthermore, an ideal compound would be inactive at sites distal to the target organ/tissues [69, 70].

There are two main methods of reducing the systemic activity of topical corticosteroids: (1) reducing gastrointestinal BIOAVAILABILITY and (2) prolonging TISSUE RESIDENCY. For example, oral administration of ileal release budesonide capsules for the treatment of Crohn's disease gives similar levels of systemic exposure to active drug, bioavailability and cortisol

suppression in adults and children as seen with prednisolone, but importantly, no clinically relevant adverse side effects were reported [71]. Alternatively, for IBD the corticosteroid can be altered to reduce gastrointestinal absorption and/or enhance first-pass hepatic metabolism. Prolonged retention in the tissue can be achieved by increasing lipophilicity, as with fluticasone propionate (FP) and fluticasone furoate (FF) and mometasone furoate, or by forming soluble intracellular fatty acid esters, as with budesonide and ciclesonide [9, 15, 63, 72, 73].

The lipophilic nature of synthetic GCs enables their rapid absorption after topical administration and helps prolong their retention in the airways [74]. When corticosteroids are delivered by inhalation, changing the inhaler device can also decrease oral delivery and subsequently gastrointestinal availability and enhance deposition in the lower airways by altering the particle size [75]. Metered dose inhalers (MDI) and dry powder inhalers (DPI) deliver 10–20% of the inhaled dose to the lungs, but >50% is deposited in the oropharynx and mouth. The drug may then be swallowed and taken up from the gut and become systemically available.

ICSs as a group all have a good therapeutic index resulting from a small particle size enabling low oral bioavailability and rapid metabolism/clearance combined with high plasma protein binding to give a short systemic half-life [10, 74]. Lipophilicity generally correlates well with absorption characteristics. For example, fluticasone (both propionate and furoate) has high lipophilicity and binding affinity for the GR, resulting in a high volume of distribution and long plasma half-life. However, the systemic side effects of fluticasone that arise from systemic absorption are limited due to its almost complete first-pass metabolism in the liver and, in the case of gastrointestinal delivery, low absorption from the gastrointestinal tract [10, 63, 74]. In general, for topical corticosteroids, treatment efficacy and side effects are directly related to tissue dose. The pharmacokinetic profile of topical corticosteroids, therefore, varies with the individual drug, the delivery mechanism and patient profile [10, 74].

32.6 Clinical Indications for Corticosteroids

Pharmacological control of inflammation may be obtained in most patients with varying doses of oral or TOPICAL corticosteroids, depending upon the disease severity [9, 15]. In most patients with asthma, COPD, IBD, allergic rhinitis and inflammatory skin diseases (such as contact dermatitis and psoriasis), adequate doses of topical corticosteroids allow systemic administration to be reduced or withdrawn completely [9, 15]. As such, corticosteroids are standard therapy for these disorders (see also Chap. 23).

Whereas in inflammatory rheumatic diseases (see Chap. 33) and in many other autoimmune diseases (e.g. systemic vasculitis) the gold standard is still represented by systemic corticosteroids, usually taken orally or parenterally during life-threatening exacerbations (flares) of these diseases.

32.6.1 Use of Corticosteroids in the Treatment of Bronchial Asthma

Asthma has long been known as a chronic inflammatory disease of the lower airways, and the beneficial effect of the potent anti-inflammatory prednisolone in asthmatic patients further emphasised this point. Treatment with prednisolone was associated with adverse side effects however. Dramatic improvements in asthma symptoms were also seen with the introduction of ICS which had few systemic side effects and systemic CORTICOSTEROID-SPARING effects. In these initial studies, only 40% of asthmatics responded well to ICS with respect to improvements in lung function—it was not investigated whether this is related to a lack of PATIENT ADHERENCE, poor inhaler technique or a true relative insensitivity to ICS [9, 15].

The routine use of ICS to prevent airway inflammation in combination with relievers such as β_2 agonists, which help the airway smooth muscle to relax after contraction, is effective in treating symptoms, reducing exacerbations and

improving lung function in most asthmatics and has resulted in great improvements in asthma control and the quality of life of most asthmatics [9, 13, 15, 61, 64]. Unfortunately a minority of asthmatics show refractoriness to GC treatment (see above and Chap. 23). In asthma, corticosteroids consistently lessen airway hyperresponsiveness (AHR) and the maximal response to a number of spasmogens and irritants. Interestingly, the reduction in airway hyperresponsiveness (AHR) may not be maximal until treatment has been given for several months. The magnitude of the reduction varies, and airway responsiveness can remain abnormal [9, 13, 15, 42, 61, 64].

As with other chronic inflammatory diseases, ICSs reduce the inflammatory markers seen in the asthmatic airways, and this results in the improvement in FEV₁ and the reversal of AHR back to levels seen in healthy non-asthmatic subjects in most subjects with mild-moderate disease. However, since discontinuation of ICS leads to a return of the symptoms of asthma and both AHR and airway inflammation to pretreatment levels, they are not a cure for asthma [9, 13, 15, 43, 61, 64].

GCs are the most successful anti-inflammatory treatment used in asthma as they target all the cells implicated in asthmatic inflammation. GCs have profound effects on infiltrating immune cells as well as on the function of airway structural cells. ICS prevents eosinophil recruitment from the bone marrow as well as their migration into the airways, and this probably explains the greater beneficial effect of oral GCs. GCs also suppress the expression of eosinophil survival factors and induce eosinophil apoptosis [9, 13, 15, 43, 61, 64].

Total blood lymphocyte numbers are reduced in asthmatic subjects who receive oral GCs. GCs can also affect CD4⁺CD25⁺ Foxp3⁺ regulatory T cell (Treg) expression and function. In comparison to the marked effects on T-cell function, ICSs have little effect on B-cell IgE production in vivo in asthma although higher doses may be effective in COPD and in vitro [9, 13, 15, 43, 61, 63, 64]. In addition, ICSs have profound effects on the function, terminal differentiation and activation status of macrophages and monocytes in asthma.

In particular, they reduce the expression of macrophage-derived pro-inflammatory cytokines and chemokines. ICS treatment reduces peripheral blood levels of monocytes and also their low affinity IgE receptor expression. ICS, by regulating DC CCR7 expression, can modulate DC migration to local lymphoid collections. Furthermore, the release of Th1- and Th2-polarising cytokines is suppressed by GCs, whilst that of IL-10 is increased [9, 13, 15, 43, 61, 64].

Overall, although most inflammatory responses in the airway are suppressed by GCs, some innate immune responses including neutrophil production and survival (GCs enhance peripheral blood neutrophilia and prevent neutrophil apoptosis), macrophage phagocytosis and airway epithelial cell survival are either unaffected or even increased. Furthermore, GCs often increase rather than suppress the expression of Toll-like receptors, complement, pentraxins, collectins, serum amyloid A (SAA) and other host defence genes [9, 13, 15, 43, 61, 64]. Despite this, a short course (at least 7 days) of systemic glucocorticoids (50 mg/daily of prednisone equivalent) is mandatory in patients with moderate-to-severe exacerbations of asthma (<https://ginasthma.org>; see also Chap. 22).

32.6.2 Use of Corticosteroids in the Treatment of Chronic Obstructive Pulmonary Disease

In contrast to asthma, glucocorticoid treatment of stable COPD is rather ineffective in reducing airway inflammation and the decline of lung function. Current national and international guidelines for the management of stable COPD patients recommend the use of inhaled long-acting bronchodilators, ICS and their combination for maintenance treatment of moderate-to-severe stable COPD (<https://goldcopd.org>) [63]. Several large controlled clinical trials of inhaled combination therapy with ICS and LABAs/ULABAs in stable COPD have shown that this combination therapy is well tolerated and produces a modest but statistically significant reduction in the

number of severe exacerbations and improvement in FEV₁, quality of life and respiratory symptoms in stable COPD patients (see also Chap. 23). In addition, the Towards a Revolution in COPD Health (TORCH) study showed a 17% relative reduction in mortality over 3 years for patients receiving salmeterol/fluticasone propionate, although this just failed to reach significance. Some patients with COPD do respond to ICS however. The Groningen and Leiden Universities Corticosteroids in Obstructive Lung Disease (GLUCOLD) study suggested that particular phenotypes of COPD benefit from fluticasone propionate $\pm$ salmeterol by reducing the rate of lung function decline. In ICS-responsive patients, the expression of genes associated with cell cycle, oxidative phosphorylation, epithelial cell signalling, p53 signalling and T-cell signalling was decreased. Overall, the long-term benefits of ICS on FEV1 decline in moderate-to-severe COPD were most pronounced in patients with fewer pack-years and less severe emphysema and inflammation [76].

Blood eosinophil counts are a promising biomarker of the response to ICS in COPD and could potentially be used to stratify patients for different exacerbation risk and reduction strategies despite we need more long-term controlled clinical trials in this area to better understand the precise cut-off of the blood eosinophil count to use for this purpose in daily clinical practice. [9, 15, 63].

A short course (at least 3 days) of systemic glucocorticoids (50 mg/daily of prednisone equivalent) is mandatory in patients with moderate-to-severe exacerbations of COPD (goldcopd.org; see also Chap. 23).

32.6.3 Use of Corticosteroids in Inflammatory Bowel Disease (IBD)

The clinical management of IBD aims to induce and maintain remission in patients with active disease. Treatment strategies are complex, consisting of pharmacological treatment and surgery depending on disease location, severity and

patients' treatment history. The traditional step-up approach consists of first-line therapy with 'conventional' or standard-of-care treatments such as aminosalicylates, corticosteroids and immunomodulators. Systemic corticosteroids are highly efficacious but burdened by side effects. Thiopurines or methotrexate can be utilised as systemic corticosteroid-sparing agents. Biologic agents targeting TNF- α remain important for systemic corticosteroid-sparing therapy in moderate-to-severe IBD [77, 78].

Topical budesonide provides an alternative to aminosalicylates when targeted to appropriate sites in the distal small bowel and colon, as do conventional corticosteroids when applied rectally [78]. At present, oral budesonide is the first-line therapy to induce remission in microscopic colitis and mild-to-moderate ileocaecal Crohn's disease patients, and oral beclomethasone is effective in treating mild-to-moderate ulcerative colitis patients with left-sided or extensive disease [79].

32.6.4 Use of Corticosteroids in Rhinology

Corticosteroids are widely used today in the field of rhinology. Allergic and non-allergic rhinitis, acute rhinosinusitis and chronic rhinosinusitis with and without nasal polyps are common diseases treated effectively with intranasal glucocorticoids, sometimes associated with intranasal histamine 1 receptor antagonists. Several studies have demonstrated the symptomatic efficacy of intranasal corticosteroids in these diseases and the prevention of nasal polyposis. Oral corticosteroids are usually reserved only to nasal polyps unresponsive to maximal pharmacological treatment with intranasal glucocorticoids associated with oral antileukotrienes [80].

There might be an improvement in symptom severity, polyp size and condition of the sinuses when assessed using CT scans in patients taking oral corticosteroids when these are used as an adjunct therapy to antibiotics or intranasal corticosteroids, but the quality of the evidence supporting this is low or very low. It is also unclear

whether the benefits of oral corticosteroids as an adjunct therapy are sustained beyond the short follow-up period reported (up to 30 days), as no longer-term data are available. More research in this area, particularly research evaluating longer-term outcomes, is required [81].

32.6.5 Use of Corticosteroids in Inflammatory Skin Diseases

Topical corticosteroids are the pillars of dermatotherapeutics with hydrocortisone being the first compound used successfully. Modifications in the basic structure generated greater *in vivo* activity, and thus a very long list of different topically active compounds is now available on the market. Apart from the classic Stoughton skin vasoconstrictor assay, various other methods are used for potency assessment of topical corticosteroids. Topical corticosteroids are classified based upon potency and action of these molecules. There is a significant evidence favouring the use of these drugs in atopic dermatitis, localised vitiligo, psoriasis, contact dermatitis and localised bullous pemphigoid. However, high-level scientific evidence in support of their use in cutaneous lichen planus, cutaneous sarcoidosis and seborrheic dermatitis is not available [82–84].

32.6.6 Use of Corticosteroids in Autoimmune Diseases

The treatment of the autoimmune inflammatory rheumatic diseases and other autoimmune conditions is covered in the chapters on disease-modifying antirheumatic drugs and on drugs for soft tissue autoimmune disorders.

Immunosuppressive therapy in combination with glucocorticoids should be used for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis according to the European League Against Rheumatism (EULAR) recommendations. For the induction of remission in life-threatening or organ-threatening disease, cyclophosphamide and rituximab are considered

to have similar efficacy; in addition, plasma exchange is recommended, where licenced, in the setting of rapidly progressive renal failure or severe diffuse pulmonary haemorrhage [85].

Immune thrombocytopenia (ITP) is characterised by immune-mediated platelet destruction and impaired production, resulting in a platelet count of less than $100,000 \text{ mm}^{-3}$ and varying degrees of bleeding risk. ITP is classified as newly diagnosed or transient (less of 3 months of thrombocytopenia), persistent (3–12 months) or chronic (>12 months) on the basis of the time since diagnosis. In primary (or idiopathic) ITP, the thrombocytopenia is isolated, whereas in secondary ITP, it is associated with other disorders (e.g., human immunodeficiency virus infection or systemic lupus erythematosus) [86]. Treatment is rarely indicated in patients with platelet counts above $50,000 \text{ mm}^{-3}$ in the absence of the following, bleeding due to platelet dysfunction or another haemostatic defect, trauma, surgery, clearly identified comorbidities for bleeding or mandated anticoagulation therapy, or in persons whose profession or lifestyle predisposes them to trauma [86].

Initial treatment for ITP is generally a course of systemic glucocorticoids, intravenous immune globulin or both. The recommended second-line treatment is splenectomy. Oral, non-peptide thrombopoietin receptor agonists (such as romiplostim and eltrombopag) are used in patients with chronic immune thrombocytopenia who have an insufficient response to glucocorticoids, intravenous immune globulin or splenectomy [86].

Oral prednisone is usually given at $0.5\text{--}2 \text{ mg/kg/day}$ until the platelet count increases ($\geq 50,000 \text{ mm}^{-3}$), which may require several days to several weeks. To avoid systemic corticosteroid-related complications, prednisone should be rapidly tapered and usually stopped in responders and especially in nonresponders after 4 weeks [86, 87]. Good response rates to systemic corticosteroid therapy range from 65% to 78% for ITP [87].

Autoimmune liver diseases coexist with rheumatic disorders in approximately 30% of cases and may also share pathogenic mechanisms. Autoimmune liver diseases result from an

immune-mediated injury of different tissues, with autoimmune hepatitis targeting hepatocytes and primary biliary cholangitis and primary sclerosing cholangitis targeting cholangiocyte. The American Association for the Study of Liver Diseases (AASLD) recommends the use of combination therapy with prednisone (or prednisolone) and azathioprine as first choice treatment. Monotherapy with prednisone is preferred in cases of pregnancy, however. For combination therapy, the induction dose of prednisone is 30 mg daily for 1 week, followed by 20 mg daily for 1 week, followed by 15 mg daily for 2 weeks. The maintenance dose is 10 mg daily until treatment is stopped. For monotherapy, a typical induction dose of prednisone is 60 mg daily for 1 week followed by 40 mg in the second week and 30 mg daily in the third and fourth week. The maintenance dose of prednisone is 20 mg daily until the endpoint or deep clinical remission. Prednisone should be tapered over time and eventually discontinued. AASLD recommends at least 3 years of treatment. Upon completion of prednisone, patients are classified as in remission, relapsed or treatment failure based on their histopathological and laboratory response to corticosteroids and the presence or absence of clinical symptoms. Mycophenolate mofetil, calcineurin inhibitors, mTOR inhibitors and biological agents are reserved for selected nonresponsive patients and administered only in experienced centres. Liver transplantation is a life-saving option for those patients who progress to end-stage liver disease [88–90].

32.6.7 Use of Corticosteroids in Inflammatory Eye Disease

Uncomplicated allergic eye disease can be managed in primary care with one or more cold compresses, lubricants, topical and/or oral antihistamines and topical mast cell stabilisers. Topical and oral corticosteroids and immunomodulatory agents should be prescribed only under the care of an ophthalmologist in refractory cases [91]. Oral corticosteroids and immunosuppression may be a preferred initial therapy

for many non-infectious, intermediate, posterior and panuveitides cases [92]. Corticosteroids are also used to prevent and reduce inflammation and the risk of complications following cataract surgery [93].

32.6.8 Use of Corticosteroids in Infections

Despite their potential to decrease the immune responses against most infectious agents (see below), corticosteroids have proven to be efficacious in the management of selected infections in controlled clinical trials.

Topical antibiotics are the best treatment for bacterial keratitis. However, outcomes remain poor with secondary corneal melting, scarring and perforation remaining. Adjuvant therapies aimed at reducing the immune response associated with keratitis include topical corticosteroids. The large, randomised, controlled Steroids for Corneal Ulcers Trial found that although corticosteroids provided no significant improvement overall, they did seem beneficial for ulcers that were central, deep or large, non-*Nocardia* or classically invasive *Pseudomonas aeruginosa*; for patients with low baseline vision; and when started early after the initiation of antibiotics. The Herpetic Eye Disease Study has also shown a significant benefit of topical corticosteroids and oral acyclovir for stromal keratitis [94].

Overall, low-quality evidence indicates that systemic corticosteroids reduce mortality among patients with sepsis. Moderate-quality evidence suggests that a long course of low-dose systemic corticosteroids reduced 28-day mortality without inducing major complications but leading to an increase in metabolic disorders [95]. There is no clear evidence that any one corticosteroid drug or treatment regimen is more likely to be effective in reducing mortality or reducing the incidence of gastrointestinal bleeding or superinfection in septic shock. Hydrocortisone delivered as a bolus or as an infusion is more likely than placebo and methylprednisolone to result in septic shock reversal [96].

In addition to antituberculous chemotherapy, systemic corticosteroids reduce mortality from tuberculous meningitis but may have no effect on the number of people who survive tuberculous meningitis with disabling neurological deficits, and the data on HIV-positive subjects are still insufficient [97]. The treatment of tuberculous pericarditis includes systemic corticosteroids, drainage and surgery. For HIV-negative patients, corticosteroids may reduce death. For HIV-positive patients not on antiretroviral drugs, corticosteroids may reduce constriction [98].

In cases of urinary tuberculosis, ureteral stenosis can deteriorate and result in ureteral obstruction during antituberculosis treatment. Pre-emptive administration of systemic corticosteroids may be beneficial for preventing such stenosis in patients with a pre-existing ureteral lesion [99].

The evidence for a benefit from systemic corticosteroid treatment of pleural tuberculosis is still inconclusive. In addition, the information on the impact of pleural tuberculosis on long-term respiratory function (potentially the most important outcome) is unknown and needs to be quantified to help decide whether further trials of corticosteroids for pleural tuberculosis are worthwhile [100].

The adjunct of systemic corticosteroids to standard care for patients hospitalised with community-acquired pneumonia (CAP) reduces time to clinical stability and length of hospital stay by approximately 1 day without a significant effect on overall mortality but with an increased risk for CAP-related rehospitalisation and hyperglycaemia [101].

The number and size of trials investigating adjunctive systemic corticosteroids for HIV-infected patients with *Pneumocystis jirovecii* pneumonia (PCP) is small, but the evidence suggests a beneficial effect for adult patients with acute respiratory failure, whereas adjunctive corticosteroids did not improve the outcome of *P. jirovecii* pneumonia in non-HIV patients [102, 103]. Aerosolized ribavirin is the first choice treatment for immunocompromised adults with respiratory syncytial virus infections, but the addition of an immunomodulator (intravenous

immunoglobulins, corticosteroids and palivizumab) may provide a survival benefit over ribavirin alone [104]. Currently there is not sufficient evidence to determine the effectiveness of corticosteroids for patients with influenza [105].

For patients with bacterial arthritis, corticosteroids are also beneficial and reduce long-term disability. Dexamethasone did not show a clear decrease in cough episodes and length of hospital stay in patients with pertussis [106]. However, corticosteroids are harmful in viral hepatitis and cerebral malaria [107].

32.6.9 Use of Corticosteroids in Other Inflammatory and Neoplastic Diseases

Low-dose hydrocortisone or a corresponding low-dose corticosteroid therapy may improve morbidity in specific target groups of critically ill patients [such as patients with acute respiratory distress syndrome (ARDS) or burns]. However beneficial effects on mortality remain to be demonstrated in large-scale randomised controlled trials [108]. There is moderate-quality evidence that suggests there is no effect of corticosteroids on critical illness polyneuropathy or myopathy (a frequent complication in the intensive care units) and high-quality evidence that corticosteroids do not affect secondary outcomes, except for fewer new shock episodes [109].

Improvements in lung function have been reported for long-term treatment with ICSs of adult patients with non-CF bronchiectasis though this study was small and not clinically relevant. Improvements in dyspnoea, wheeze and cough-free days are reported in small trials of ICSs and ICS/LABA combinations for the same patients [110].

Primary therapy of allergic bronchopulmonary aspergillosis (ABPA) consists of oral corticosteroids to control exacerbations, itraconazole as a systemic corticosteroid-sparing agent and optimised asthma therapy [111].

Oral corticosteroid treatment of patients with sarcoidosis improves the chest X-ray symptoms and spirometry over 3–24 months. However,

there is little evidence of an improvement in lung function. There are limited data beyond 2 years to indicate whether oral corticosteroids have any modifying effect on long-term disease progression. For these reasons oral corticosteroids may be of benefit for patients with stage 2 and 3 sarcoidosis with moderate-to-severe or progressive symptoms or chest X-ray changes [112].

Most patients with sarcoidosis are not disabled by their illness, so the decision to provide treatment should reflect a weighing of the risks of using corticosteroids, the most common therapy, against the potential benefits. A general rule is to consider instituting treatment when organ function is threatened. Detection of granulomatous disease on physical examination, biopsy, imaging studies or serologic testing is not a mandate to provide treatment. Systemic corticosteroids remain the first-line treatment. Other immunosuppressive agents may be considered for the patients who respond poorly to corticosteroids or who experience significant adverse effects. An international expert panel has suggested initiating treatment with oral prednisone at a dose of 20–40 mg/day. The panel recommends evaluating the response to treatment after 1–3 months. If there has been a response, the prednisone dose should be tapered to 5–15 mg/day, with treatment planned for an additional 9–12 months. Lack of a response after 3 months suggests the presence of irreversible fibrotic disease, nonadherence to therapy or an inadequate dose of prednisone [113, 114].

Neurological and cardiac involvement in sarcoidosis are rare but two of the major causes of death in these patients. One-third of patients with neurosarcoidosis do not respond to treatment with systemic corticosteroids or other therapies [115]. There is a clear need for large multicentre prospective registries and trials in patients with cardiac sarcoidosis [116].

At present, there is no evidence for an effect of corticosteroid treatment in patients with idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) [117]. In contrast, the prognosis of nonspecific interstitial pneumonia (NSIP) is good compared with IPF/UIP, because usually

these patients respond to systemic corticosteroids and/or immunosuppressive agents [118].

Because corticosteroids act through a variety of mechanisms to inhibit eosinophil function and induce apoptosis, they are first-line therapy for primary (or idiopathic) eosinophilic lung diseases, including primary acute eosinophilic pneumonia, primary chronic eosinophilic pneumonia (Carrington's disease), eosinophilic granulomatosis with polyangiitis [(EGPA), also known as Churg-Strauss syndrome] and primary hypereosinophilic syndrome (IHES). In these disorders elevated levels of activated eosinophil in the lung tissue lead to inflammation and tissue damage [119].

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is a complex immunopathological pulmonary syndrome caused by inhalation of a wide variety of antigens to which the individual has been previously sensitised. The treatment of first choice is represented by the avoidance of inciting antigens. Systemic corticosteroids may be useful in acute episodes for symptomatic relief or in chronic and progressive disease, but their long-term efficacy has never been validated in prospective clinical trials [120].

Langerhans cell histiocytosis (LCH) limited to the lungs is low-grade histiocytic neoplasm and usually responds well to complete smoking cessation. The current standard of care for multi-system LCH is empirically derived chemotherapy with vinblastine and prednisone but cures fewer than 50% of patients, and optimal therapies for relapse and neurodegenerative disease remain uncertain [121].

In patients with lung cancer, drug-induced interstitial lung disease has a more unfavourable outcome but requires higher-dose systemic corticosteroid therapy as compared with those with radiation-induced pneumonitis [122].

There are short-term benefits in using systemic corticosteroids for the symptomatic treatment of cancer-related fatigue and anorexia cachexia in advanced incurable cancer. Future studies are needed to determine the optimal dose, the type and the role of corticosteroid rotation so as to optimise long-term efficacy and minimise side effects [123].

32.7 Side Effects of Corticosteroid Therapy

Overall, the duration, dosage and dosing regime, the particular corticosteroid used and its mode of administration along with the patient's individual susceptibility appear to determine the incidence of adverse events. Not surprisingly, side effects are much more severe with systemic corticosteroid use, although even topical application can induce both local and systemic side effects (Table 32.1). When corticosteroids are administered by systemic routes over a long period of time at reasonably high concentrations, their beneficial effects are often overshadowed by a number of side effects (iatrogenic Cushing syndrome) [124].

Side effects of oral corticosteroids include skin and muscle atrophy, delayed wound healing and increased risk of infections, OSTEOPOROSIS and bone necrosis, glaucoma and cataracts, behavioural changes, hypertension, peptic ulcers, gastrointestinal bleeding and diabetes mellitus. Interestingly, it appears that early skin atrophy induced by corticosteroid therapy is reversible, whereas major atrophy leading to striae formation is not [124]. These side effects often occur together, and this is exemplified by Cushing's syndrome (hypercortisolism), the signs and symptoms of which include elevated systemic arterial blood pressure, development of diabetes mellitus, pink-to-purple striae (stretch marks) on the abdominal skin, fatigue, depression, moodiness and accentuated accumulation of fatty tissue on the face and upper back (Buffalo hump). Women with Cushing's syndrome often have irregular menstrual periods and develop new facial hair growth. Men may show a decrease in sex drive [9].

Commonly cited side effects associated with long-term systemic corticosteroid exposure included systemic arterial hypertension (prevalence >30%); bone fractures (21–30%); cataract (1–3%); nausea, vomiting, and other gastrointestinal conditions (1–5%); and metabolic issues (e.g. weight gain, hyperglycaemia and type 2 diabetes mellitus where cases had fourfold risk of controls). However, the association of dose and

Table 32.1 Potential tissue-/organ-specific side effects of topical and/or systemic corticosteroids

<i>Cardiovascular system and metabolism:</i>
Systemic arterial hypertension
Dyslipidaemia (increased VLDL and/or LDL serum levels)
Hypercoagulability with thrombosis
<i>Central nervous system:</i>
Disturbances in mood, behaviour, memory and cognition, appetite increase
Decreased fatigue, "steroid psychosis", steroid dependence
<i>Endocrine and renal systems:</i>
Iatrogenic Cushing's syndrome
Iatrogenic diabetes mellitus
Iatrogenic Addison's disease
Growth retardation
Hypogonadism, delayed puberty
Increased sodium retention and potassium excretion
<i>Eye:</i>
Glaucoma
Cataract
<i>Gastrointestinal:</i>
Peptic ulcer
Increased risk of gastrointestinal bleeding
Hepatic steatosis
Acute pancreatitis
<i>Immune system:</i>
Increased risk of infections
Re-activation of latent viral (varicella-zoster virus), bacterial (<i>M. tuberculosis</i>) or helminthic (<i>S. stercoralis</i>) infections
<i>Skeleton and muscle:</i>
Muscle atrophy/myopathy
Osteoporosis and bone fractures
Bone necrosis
<i>Skin and subcutaneous:</i>
Weight gain, skin thinning, striae rubrae
Delayed wound healing
Steroid acne, perioral dermatitis
Erythema, telangiectasia, purpura, hypertrichosis
<i>Adipose tissue:</i>
Adipose tissue expansion and redistribution [visceral obesity, subcutaneous localised adiposity (buffalo hump)]

VLDL very-low-density lipoproteins, LDL low-density lipoproteins

duration with increased adverse effect risk is not well-quantified [125]. Systemic glucocorticoid long-term use is also associated with an increased risk of bacterial, fungal and viral infections, including tuberculosis, disseminated strongyloidiasis and hepatitis B virus and hepatitis C virus

reactivation. Patients with undiagnosed and untreated HIV infection may be at increased risk of developing infectious complications with the initiation of chronic glucocorticoid therapy [126].

Patients with conditions necessitating moderate or high doses of systemic corticosteroids (≥ 20 mg/day of prednisone) for >2 weeks should be asked about vaccination history to ensure that they are up to date on the following vaccinations: *Haemophilus influenzae* B; hepatitis A virus (HAV) and HBV; human papillomavirus; influenza; *Neisseria meningitidis*; measles, mumps and rubella (MMR); *Streptococcus pneumoniae*; and tetanus. Patients >50 – 60 years of age (with or without a history of varicella-zoster virus infection) who have not received the varicella-zoster virus vaccine should receive it, if possible, at least 2–4 weeks before the initiation of moderate- or high-dose systemic glucocorticoids. Patients taking ≤ 20 mg prednisone per day (or the equivalent) can safely receive the zoster vaccine at any time [126]. In addition, invasive aspergillosis is increasingly found in COPD patients during exacerbations treated with systemic corticosteroids [127].

All currently available topical corticosteroids are absorbed into the systemic circulation and, therefore, inevitably have some systemic effect, although this is considerably less than those seen with systemic corticosteroids (Table 32.1). The occurrence and severity of the side effects seen depend upon the duration of use, dosage, dosing regime and specific drug used, along with individual patient variability. However, the highest risk factor appears to be prolonged use. Side effects of topical corticosteroids are tissue-dependent and include glaucoma, cataracts, tissue atrophy and delayed wound healing, whilst at high doses, there is an increased risk of local and systemic infections, adrenal suppression (iatrogenic Addison's disease) and osteoporosis (and bone fractures). The growth retardation seen with oral corticosteroids does not appear to be a problem with modern topical corticosteroids, although there may be an initial reduction in growth velocity on starting therapy [125]. Currently, most patients with asthma and COPD are treated with ICSs, whereas the systemic preparations are being

limited to patients with severe asthma or during exacerbations of these diseases which reduces the incidence of side effects (see above and Chap. 23).

Modern inhaled GCs (ICS) have high receptor affinity, are retained in the airways and are rapidly metabolised after absorption from the gastrointestinal tract which accounts for their good safety profile even when used in more severe asthmatics and at high nebulised doses during exacerbations of asthma or COPD. The side effects seen with ICSs are usually limited to oropharyngeal candidiasis and/or dysphonia. In general, ICS treatment efficacy and side effects are directly related to tissue dose although there is some evidence that this may vary with the drug and patient profile [9, 15].

The incidence of pneumonia is slightly increased in COPD patients treated with inhaled glucocorticoids compared to placebo in most studies, regardless of the type of glucocorticoid inhalation used, suggesting a class effect. Older age, low body mass index, low FEV₁ and being a current smoker are all factors variously associated with increased risk of pneumonia [128]. Compared with non-ICS treatment, ICS treatment also seems associated with a significantly higher risk of tuberculosis (OR, 2.29) but not influenza. The number needed to harm to cause one additional tuberculosis event is lower for patients with COPD treated with ICSs in endemic areas than for those in nonendemic areas (909 vs. 1667, respectively) [129]. Furthermore, ICS use may increase the risk of upper respiratory tract infection (URTI) in patients with COPD, but this should be further investigated [130].

Second-generation intranasal corticosteroids have pharmacokinetic characteristics that minimise their systemic bioavailability, resulting in minimum risk for systemic adverse events [80].

Guidelines for the management of asthma recommend the continued use of ICSs in pregnancy, with budesonide having a particularly good safety profile. Recent data suggest small effects of asthma and/or asthma medication use on congenital malformations; however, there is less data available on the safety of ICS/LABA combinations, which are increasingly used for maintenance treatment [131]. The risk-benefit ratio

should always be considered before prescribing any intranasal corticosteroid sprays during pregnancy. Lacking sufficient clinical trials on the use of intranasal corticosteroid sprays in pregnancy, it has been suggested that the intranasal use of fluticasone furoate, mometasone and budesonide is safe if they are used at the recommended therapeutic dose after a proper medical evaluation. Intranasal fluticasone propionate might also be a safe option in the absence of other intranasal corticosteroids [132].

Similarly, no association between maternal use of topical corticosteroids for dermatological use of any potency and an increase in adverse pregnancy outcomes, including mode of delivery, congenital abnormality, preterm delivery, foetal death and low Apgar score, have been noted. However a probable association between low birth weight and maternal use of potent to very potent skin topical corticosteroids, especially when the cumulative dosage of topical corticosteroids throughout the pregnancy is very large, warrants further investigation [133]. Besides, evidence clearly advocates judicious use of mild-to-moderate topical corticosteroids for dermatological use (if required) in pregnancy and lactation, and there is no risk of any foetal abnormality [133].

In dermatology, 'steroid phobia' is still a considerable concern in connection with topical corticosteroids, particularly with regard to skin thinning (the more potent drugs) and systemic absorption with effects on growth and development. Tachyphylaxis and allergic contact dermatitis (due to a delayed type allergic reaction) are the real potential problems in clinical practice when using topical corticosteroids for dermatological diseases [83, 84, 134]. It should also be noted that rare allergic hypersensitivity to topical corticosteroids applied to other sites than skin and even to systemic corticosteroids has been described [134].

Taken together, the side effects seriously limit the value of long-term treatment with systemic corticosteroids in severe inflammation where the risk/benefit ratio is compromised. This has driven the need to develop novel agents with the anti-inflammatory capacity of corticosteroids but with reduced side effects.

While the major anti-inflammatory effects of corticosteroids are almost certainly due to transrepression, the underlying molecular mechanisms for the side effects of corticosteroids are complex and not fully understood. Certain side effects such as diabetes mellitus and glaucoma are due to transactivation events, whilst others are due to transrepression (hypothalamic-pituitary axis, HPA, suppression). In addition, the precise molecular events underlying corticosteroid induction of osteoporosis is unclear but probably requires both gene induction and gene repression.

Despite this uncertainty, there has been a search for 'dissociated' corticosteroids that selectively transrepress without significant transactivation, thus potentially reducing the risk of systemic side effects. Several SEGRAMs have been reported which show dissociated properties in human cells and are now in clinical development, showing good separation between transrepression and transactivation actions in the skin. This suggests that the development of SEGRAMs with a greater margin of safety is possible and may even lead to the development of oral compounds that have reduced adverse effects. Furthermore, the newer inhaled corticosteroids used today, such as fluticasone (both propionate and furoate), mometasone and budesonide, appear to have more potent transrepressing than transactivating effects, which may account, at least in part, for their selection as potent anti-inflammatory agents [9, 15]. These new potent corticosteroids are particularly effective as topical agents, and their use has overtaken that of oral/systemic corticosteroids for many diseases. An alternative approach to obtain safer drugs is the use of soft drugs, such as ciclesonide, which are only activated at the site of inflammation. Ciclesonide is a novel inhaled corticosteroid for the treatment of asthma. Ciclesonide itself is inactive and needs to be cleaved by lung-specific esterases in order to bind to the GR. According to data from healthy volunteers and asthma patients, ciclesonide affects serum cortisol levels significantly less compared to beclomethasone dipropionate or fluticasone propionate, indicating that ciclesonide might have less systemic effects and hence a superior safety profile [9, 15].

32.8 Summary

Corticosteroids are the most effective therapy for chronic immune and inflammatory diseases in current use. Despite their success over the past 70 years, and especially since the advent of new potent halogenated compounds, worries about the detrimental side effects of systemic corticosteroids have limited their long-term use. This has resulted in the increasing use of topical corticosteroids targeted to the site of inflammation rather than systemic administration. Improvements in risk/benefit ratios are likely to occur, as greater understanding of the role of chemical substitution of the synthetic corticosteroids becomes clear and more potent tissue selective drugs are developed. Drugs that target distinct aspects of corticosteroid function, switching on or off genes, are also under development and, along with non-steroidal agents that target different aspects of the inflammatory response, are likely to lead to safer drugs with a much reduced side effect profile. However, until these become widely available, current systemic and topical corticosteroids are likely to remain the major treatment for most acute and chronic inflammatory diseases.

Recommended Websites

<https://www.ncbi.nlm.nih.gov/pubmed>
<http://www.cochranelibrary.com/>

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