CHAPTER 42

Glucocorticoids

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- Glucocorticoids (GCs) have powerful anti-inflammatory and immunomodulatory effects and are useful for treating many rheumatic diseases.
- Glucocorticoids work by inhibiting leukocyte access to inflamed tissues, interfering with the function of cells involved in the inflammatory process, and suppressing the production of humoral factors such as cytokines and prostaglandins involved in immune inflammatory processes.
- Glucocorticoids accomplish their effects by several mechanisms, including altering synthesis of proteins, releasing proteins from intracellular protein complexes that include GC receptors, and changing the properties of biological membranes.
- Initial GC dosage should be determined by the type and severity of the disease manifestation under treatment.
- Because of significant toxicity associated with long-term GC use, doses of <7.5 mg daily are recommended only if required to control symptoms.

Glucocorticoids (GCs) have been in use for more than 50 years. They are powerful and cost-effective drugs with strong anti-inflammatory and immunomodulatory effects that are used to treat rheumatic and other diseases. Their therapeutic use has increased continuously in recent years (1,2). Furthermore, our understanding of the action of glucocorticoids has advanced in recent years, especially with regard to mechanisms of action, clinical usage, side-effect potential, and the development of new glucocorticoid drugs (2–5). GCs are the subject of this chapter as the terms *corticosteroids* or *corticoids* do not precisely designate these compounds. The adrenal cortex indeed synthesizes glucocorticoids, but also mineralocorticoids and androgens. The term *steroids*, although often used (e.g., in steroid-induced osteoporosis), is similarly incorrect because it simply describes chemical compounds characterized by a common multiple-ring structure which include cholesterol and sex hormones.

MECHANISMS OF ACTION

Cellular Effects on Immune Cells

Glucocorticoids mediate important anti-inflammatory and immunomodulatory effects when used therapeutically. There are many specific effects of the commonly used GC drugs, which include prednisone, prednisolone, methylprednisolone, and dexamethasone. However, for daily practice we can summarize their clinical actions as follows:

- Inhibit leukocyte traffic and access of leukocytes to the site of inflammation
- Interfere with functions of leukocytes, fibroblasts, and endothelial cells
- Suppress the production and actions of humoral factors involved in the inflammatory process

Virtually all primary and secondary immune cells are more or less affected. The most important effects on the different cell types are listed in Table 42-1.

Molecular Mechanisms

Four different mechanisms have been identified to date. The interested reader can find more details in recent reviews (2,3). Cytosolic GC receptor (*cGCR)-mediated genomic effects* refers to the classical mechanism by which GCs up- or downregulate the synthesis of specific regulatory proteins. The GC molecules bind to the cGCR alpha. The activated GC/cGCR complex in turn binds to specific DNA-binding sites called *glucocorticoid responsive elements*. In some cases, this results in upregulated synthesis of certain proteins. This process, called *transactivation*, affects between 10 and 100 genes per cell that are regulated in this way (6). There are also

TABLE 42-1. IMPORTANT EFFECTS OF GLUCOCORTICOIDS ON PRIMARY AND SECONDARY IMMUNE CELLS.

Monocytes/macrophages
↓ number of circulating cells (↓ myelopoiesis, ↓ release)
↓ expression of MHC class II molecules and Fc receptors
↓ synthesis of proinflammatory cytokines (e.g., IL-2, IL-6, TNF-alpha) and prostaglandins
T cells
↓ number of circulating cells (redistribution effects)
↓ production and action of IL-2 (most important)
Granulocytes
↓ number of eosinophil and basophil granulocytes
↑ number of circulating neutrophils
Endothelial cells
↓ vessel permeability
↓ expression of adhesion molecules
↓ production of IL-1 and prostaglandins
Fibroblasts
↓ proliferation
↓ production of fibronectin and prostaglandins

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ABBREVIATIONS: IL, interleukin; MHC, major histocompatibility complex; TNF, tumor necrosis factor.

negative glucocorticoid responsive elements, but inhibitory effects are typically mediated instead by negative interference of the GC/cGCR complex with transcription factors such as NF-κB and activator protein 1 (AP-1). Via this latter mechanism, GCs downregulate the synthesis of proinflammatory cytokines, such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-alpha). Many genes are regulated via this mode of action, which is termed *transrepression*. Altogether, it is estimated that GCs influence the transcription of approximately 1% of the entire genome (7).

With respect to the regulation of genomic GC actions, it must be mentioned that an alternative splice variant of the cGCR alpha exists, the cGCR beta isoform. This isoform does not bind ligand and may inhibit classic cGCR alpha–mediated transactivation of target genes (2,8).

Recently, it became evident that GCs also mediate effects via so called *cGCR-mediated nongenomic effects*. Croxtall and colleagues have suggested that following GC binding the GC/cGCR complex mediates not only classical genomic actions, but ligand binding also initiates a rapid release of proteins (chaperones and co-chaperones such as Src) from the multiprotein complex that includes the cGCR. These (co-)chaperones are considered to be responsible for producing measurable effects within a few minutes, far more rapidly than genomic effects (9).

Glucocorticoids also mediate rapid and therapeutic relevant effects via membrane-bound GCR (mGCR) termed *mGCR-mediated nongenomic effects* (2). mGCRs have been recently identified on human PBMC from healthy controls. A strong positive correlation between the frequency of mGCR-positive monocytes and various parameters of disease activity was found in patients with rheumatoid arthritis (RA). One of the suggested functions of mGCR is to mediate cell lysis by inducing apoptosis. Therefore, it is currently assumed that mGCR mediates a negative feedback regulation as follows: Immunostimulation (or high disease activity) induces mGCR expression on immune cells, such as monocytes. This in turn leads to a significantly higher percentage of cells undergoing GC-induced apoptosis, which ameloriates the activity of the immune system. This mechanism remains speculative and further experiments are needed to confirm the functional activity of mGCR (2).

Finally, GCs at high concentrations are able to intercalate into cellular membranes, such as plasma and mitochondrial membrane, and change their properties. This is the basis for *nonspecific nongenomic effects*, possibly mediated by changes in the cation transport through the plasma membrane and in the proton leak of the mitochondria. These physicochemical interactions with biological membranes are very likely to be the key to the very rapid immunosuppressive and anti-inflammatory effects of high dose GCs. Very high GC concentrations are achieved by intra-articular GC injections or intravenous GC pulse therapy.

THERAPEUTIC USE

Most of the desired clinical effects of GC treatment in rheumatic patients are mediated by transrepression. These include the reduction of clinical signs and symptoms of inflammation and the retardation of the radiological progression in rheumatoid arthritis.

Inhibition of Inflammation

An inflammatory process (e.g., arthritis, myositis) is usually characterized by upregulated synthesis of inflammatory mediators, such as prostaglandin E_2 (PGE_2) and cytokines. Among the most important clinical effects of GCs are reduced synthesis of enymes involved in the biosynthesis of PGE_2 (see Chapter 41) and proinflammatory cytokines, such as IL-1 and TNF-alpha. This is accomplished by transrepression that finally leads, usually within hours or a few days depending on the dosage applied, to the well-known and striking relief from signs and symptoms of inflammation, including pain.

Retardation of Radiographic Progression

The ability of GC to retard radiological progression in RA was first demonstrated by Kirwan (10). In 1997, Boers and colleagues published a multicenter, double-blind, randomized trial (COBRA), in which patients with early RA were randomized to either step-down therapy with two disease-modifying antirheumatic drugs (DMARDs; sulfasalazine and methotrexate) and prednisolone (start 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day and stopped at 28 weeks), or sulfasalazine alone. In the combined drug strategy group, a statistically significant and clinically relevant effect in retarding joint damage was shown compared with the effect of sulfasalazine alone (11). In an extension of this study, long-term (4–5 years) beneficial benefits were also shown regarding radiological damage following the combination strategy (12). These data were later supported by other studies, with some of them very recently published (13–15).

Proinflammatory cytokines such as IL-1 and TNF-alpha are key players in the process of joint damage in RA. They stimulate osteoblasts and T cells to produce RANKL which bind to RANK on osteoclast precursor cells and on mature osteoblasts. This finally leads to more activated osteoclasts, which are responsible for bone resorption/erosions in RA. The ability of GCs to reduce the synthesis of these proinflammatory cytokines via transrepression may contribute to their effects on radiological progression in RA.

Glucocorticoid Use in Daily Practice

The basis for the use of different GC dosages in different clinical conditions is essentially empirical, as the evidence to support preferences in specific clinical settings is remarkably scarce (5). It is clear, however, that the GC dosages used are proportionately higher in patients with increased clinical activity and with increased severity of the disease under treatment. The rationale for this (mostly successful) clinical decision is the following: (i) Higher dosages increase cGCR saturation in a dose-dependent manner which intensifies the therapeutically relevant, *genomic* GC actions discussed above; (ii) it is assumed that with increasing dosages the *nongenomic* actions of GCs increasingly come into play (2).

Over the last few decades, clinicians in their daily practice had already created landmark GC doses that were still cloudy in their definition but clearly grouped around 7.5, 30, and 100 mg prednisolone equivalent per day. As a result of a consensus conference, in 2002 recommendations on standardized nomenclature for GC doses and GC treatment regimens were published (Table 42-2) (5).

TABLE 42-2. STANDARDIZED NOMENCLATURE FOR GLUCOCORTICOID DOSES AND GLUCOCORTICOID TREATMENT REGIMENS.

TERMINOLOGY	DOSAGE[a]	CLINICAL APPLICATION	GENOMIC ACTIONS (RECEPTOR SATURATION)	NONGENOMIC ACTIONS	ADVERSE EFFECTS
Low dose	≤7.5	Maintenance therapy for many rheumatic diseases	+ (<50%)	?	Relatively few
Medium dose	>7.5 to ≤30	Initially given in primary chronic rheumatic diseases	++ (>50% to <100%)	(+)	Dose-dependent and considerable if treatment is given for longer periods
High dose	>30 to ≤100	Initially given in subacute rheumatic diseases	++ (+) (almost 100%)	+	Cannot be administered for long-term therapy because of severe side effects
Very high dose	>100	Initially given in acute and/or potentially life-threatening exacerbations of rheumatic diseases	+++ ([almost] 100%)	++	Cannot be administered for long-term therapy because of dramatic side effects
Pulse therapy	≥250 for one or a few days	Particularly severe and/or potentially life-threatening forms of rheumatic diseases	+++ (100%)	+++	High proportion of cases with a relatively low incidence of side effects

[a] Dosage is given in milligrams of prednisone equivalent per day.
Data from references 2 and 5.

TABLE 42-3. SUGGESTED MECHANISMS MEDIATING GLUCOCORTICOID RESISTANCE IN RHEUMATIC DISEASES (SELECTION).

Reduced number of GCR and/or reduced affinity of the ligand
Polymorphic changes and/or overexpression of chaperones/co-chaperones
Increased expression of inflammatory transcription factors
Changes in the phosphorylation status of the GCR
Overexpression of GCR beta
Multidrug resistance gene MDR1
Alteration in the expression of membrane bound GCRs (mGCRs)

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ABBREVIATIONS: GCR, glucocorticoid receptor.

Glucocorticoid Resistance

Glucocorticoid resistance in RA is not well defined. However, in routine daily practice the loss of symptomatic relief over time is considered to be a sign of GC resistance (6). By this definition, over 30% of patients with RA become resistant after 3 to 6 months. The current knowledge of the molecular basis for GC resistance in the rheumatic diseases is summarized in Table 42-3. It should be noted that GC resistance in the sense defined above is different from a specific disease entity, called familial/sporadic GC resistance, a rare condition defined as generalized, partial target-tissue resistance to GCs. In this disease, several different hereditary mutations in the GCR gene have been identified which impair normal signal transduction (6).

ADVERSE EFFECTS

Apart from their desired clinical actions, GCs unfortunately also have pleiotropic effects causing a number of adverse reactions which limit their clinical use, especially at higher dosages and for longer time periods (Table 42-2). A critical and pragmatic overview of scientific evidence on the adverse effects of GCs given at lower dosages (⩽10 mg/day prednisolone equivalent) in RA has been recently published (16). As one key message, safety data from recent randomized, controlled clinical trials of low-dose glucocorticoid treatment in RA suggest that adverse effects associated with these lower GC dosages are modest, and are often not statistically different from those of placebo.

Musculoskeletal Adverse Effects

Glucocorticoids are the most common cause of secondary *osteoporosis*. The incidence of osteoporosis is time- and dose-dependent, but there is no consensus about a safe dose. Although some studies suggest that doses of 7.5 mg of prednisone a day or less are relatively safe, a longitudinal study observed an average loss of 9.5% from spinal trabecular bone over 20 weeks in patients exposed to 7.5 mg of prednisolone per day. It should be noted, however, that in cases of inflammatory diseases, such as RA, osteoporosis is multifactorial. Beside the use of GCs, there are other factors that promote the development of osteoporosis, including decreased physical activity, duration of disease, and disease activity (1,17). In parallel, disease-independent risk factors such as age, gender, genetic predisposition, nutritional factors, endocrine changes, or body weight must be considered (1). Nonetheless, osteoporosis is probably the most common adverse effect of chronic low-dose GC therapy. Strategies for the prevention and treatment of GC-induced osteoporosis are well established (see Chapter 35).

In patients treated with low doses of GCs, *osteonecrosis* is uncommon. For GCs at higher dosages it is still a matter of debate to what extent GCs and/or the underlying disease, respectively, contribute to the pathogenesis of osteonecrosis. Although quite often suspected, *myopathy* is currently believed to be exceedingly rare with GC doses of <7.5 mg prednisolone equivalent daily.

Endocrine and Metabolic Adverse Effects

In patients without preexisting abnormalities of glucose tolerance, GC dose-dependently cause increased fasting glucose levels and a more pronounced increase of postprandial values. Patients with risk factors for the development of diabetes mellitus, including family history, increased age, obesity, and previous gestational diabetes mellitus, are at increased risk of developing new-onset hyperglycemia during GC treatment. This is usually rapidly reversible when GCs are stopped, but some patients will go on to develop persistent diabetes.

One of the most notable effects of chronic endogenous and exogenous GC excess is the *redistribution of body fat* and the *increase of body weight*. Centripetal fat accumulation with sparing of the extremities is a characteristic feature of patients exposed to long-term therapy with GCs.

Cardiovascular Adverse Effects

Glucocorticoids induce *dyslipidemia,* whereas their role in *atherosclerosis* is controversial. Higher dosages of GCs are considered to contribute to the development of *cardiovascular disease*, but evidence is currently lacking to show that low-dose GCs significantly increase the incidence of *cardiovascular disease* in RA. Because

synthetic GCs have little mineralocorticoid effects, their potential to induce *hypernatraemia, hypokalaemia*, and *sodium and water retention* is low at low doses. Nonetheless, induction of *hypertension* is seen in about 20% of patients exposed to exogenous GC. The mechanisms involved have not been fully elucidated, but it is suggested that GC-induced hypertension is dose-related and is less likely with medium or low-dose treatment. Incidences of *arrhythmia* and *sudden death* are rare and mostly limited to patients receiving high-dose pulse GC.

Dermatological Adverse Effects

Clinically relevant adverse effects on the skin include iatrogenic *Cushing's syndrome*, *catabolic effects* (cutaneous atrophy, purpura, striae, easy bruisability, and impaired wound healing), *steroid acne*, and *hair effects*. Cushingoid appearance, purpura, and easy bruisability is seen in over 5% of the patients exposed to $\geqslant$5 mg prednisone equivalent for $\geqslant$1 year.

Ophthalmological Adverse Effects

Long-term use of systemic GCs may induce formation of posterior subcapsular *cataract* attributed to GCs. In a group of patients with RA treated with 5 to 15 mg/day prednisone for a mean of 6 years, 15% were found to have cataracts, compared with 4.5% of matched RA controls not using prednisone. Systemic GCs also increase the risk of *glaucoma*. In the general population, 18% to 36% of those exposed to GCs had an increase in intraocular pressure. The incidence of this adverse effect tends to be higher in families, suggesting a genetic basis. Patients with preexisting glaucoma are especially sensitive and will have this condition aggravated upon exposure to GCs.

Gastrointestinal Adverse Effects

The overall estimated relative risk for *gastrointestinal ulcer disease* among current GCs users has been reported to be 2.0. However, the increased risk was almost completely due to cotreatment with nonsteroidal anti-inflammatory drugs (NSAIDs; see Chapter 41). The relative risk for patients comedicated with NSAIDs was 4.4, but for those receiving GCs alone there was no significantly increased risk (1.1).

Infectious Adverse Effects

The use of GCs is associated with increased susceptibility to various viral, bacterial, fungal, and parasitic infections. In a meta-analysis of 71 trials involving over 2000 patients with different diseases and different dosages of GCs, a relative risk of infection was found to be 2.0. Therefore, physicians should anticipate the risk of infections with both usual and unusual organisms, realizing that GCs may blunt the classic clinical features and delay the diagnosis.

Psychological and Behavioral Disturbances

It has become consensus in the literature that the overall incidence of GC-induced *psychosis* is 5% to 6%. However, most cases are associated with high doses of GCs and an influence of the underlying disease, such as systemic lupus erythematosus (SLE), is often difficult to rule out. GC treatment has been associated with a variety of *minor mood disturbances* such as depressed or elated mood, irritability or emotional lability, anxiety and insomnia, and memory and cognition impairments. The exact incidence of such symptoms in rheumatic patients exposed to common doses of GCs is not known, but doses of < 20 to 25 mg prednisone equivalent per day are associated with few or no significant disturbances.

NEW GLUCOCORTICOID RECEPTOR LIGANDS IN THE PIPELINE

Over the last five decades, strategies such as intra-articular injections or optimized dosing regimens have been developed to improve the benefit/risk ratio (4). A new approach is the targeted delivery of conventional glucocorticoids using liposomes. Liposomes are small vesicles approximately 100 nm in size, which are used as a carrier system for GC drugs. These liposomes have been reported to accumulate selectively at the site of inflammation (18). Consequently, very high local concentrations of GCs are achieved, as, for example, in the inflamed joint. It has been recently shown in mice that liposomal prednisolone phosphate is able to produce a strong and sustained resolution of joint inflammation (18). Other current approaches to optimize the therapy with conventional GC drugs are formulations to change the timing of glucocorticoid delivery ("timed-release tablet formulation"). Also, the investigation of glycyrrhetinic acid as a potential drug needs to be mentioned here. This substance inhibits 11-beta-hydroxysteroid dehydrogenase and increases the levels and thus the action of endogenous glucocorticoids.

It seems, however, that efforts with conventional GC drugs have almost reached their limits (4). Further improvement will require qualitatively new drugs, which are currently under development. The intensive research to develop innovative novel GC receptor ligands with a clearly improved therapeutic ratio has yielded at least two promising developments to date. The first develop-

ment concerns the so-called nitrosteroids. These agents are structurally characterized by an aliphatic or aromatic molecule which links a conventional GC drug with nitric oxide (NO). Drugs such as NO-prednisolone or NO-hydrocortisone slowly release NO which synergistically enhances anti-inflammatory effects and induces less osteoporosis than prednisolone in animal models (19). The second group of new agents are the selective glucocorticoid receptor agonists (SEGRAs) or "dissociating glucocorticoids." As a background, it has become evident over the last few years that many adverse effects of GCs are predominantly caused by the transactivation mechanism (e.g., diabetes, glaucoma), whereas anti-inflammatory effects are mediated mostly by transrepression mechanisms (e.g., inhibition of the synthesis of proinflammatory cytokines and prostaglandin biosynthetic enzymes) (2,20,21). SEGRAs induce predominantly the desired transrepression effects while having reduced undesirable transactivation activity as compared with conventional GC drugs (22,23). A recent report showed a drug of this class to have effective anti-inflammatory actions but to be accompanied by reduced adverse effects, such as increased body weight and skin atrophy, in animal experiments (21).

In summary, results of research over the past few years have greatly increased our knowledge of GCs as the most effective anti-inflammatory agents available. In particular, novel findings on mechanisms of action and new information on dose/effect relationships have stimulated intensive research activity with the aim of bringing increased knowledge from scientific research into clinical use as quickly as possible. There are promising approaches aimed at developing new GC receptor ligands that may improve the benefit/risk ratio and well-being of patients with rheumatic diseases.

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