GLUCOCORTICOIDS

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INTRODUCTION

Steroid hormones are essential constituents of the intercellular communication system in higher organisms[1]. Glucocorticoids (GCs) are a major subclass of steroid hormones that modulate a large number of metabolic, cardiovascular, immune, and behavioral functions[2-4]. GCs are produced by the adrenal cortices under the regulatory influence of adrenocorticotropic hormone (ACTH), which is secreted by pituitary corticotrophs under the regulatory influence of hypothalamic corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)[1-3]. The hypothalamic-pituitary-adrenal (HPA) axis is kept in balance by the negative feedback effects of cortisol, the major GC, on the secretion of ACTH and CRH[2]. At the resting state, basal levels of CRH, AVP, ACTH, and cortisol are released in a pulsatile and circadian manner; at this state, cortisol helps sustain normoglycemia and a normal arterial blood pressure[2]. During physical and/or emotional stress (i.e., in the stress state), the adaptive activation of the HPA axis and the resultant increase in cortisol levels are required for stimulation of the central nervous system (CNS) and for achieving higher blood glucose levels and blood pressure[1]. Cortisol also modulates and restrains a potential concurrent inflammatory/immune reaction, which otherwise might lead to tissue damage[2].

Natural GCs have some mineralocorticoid activity through cross-interaction with the mineralocorticoid receptor. To avoid complications from the latter activity, synthetic compounds with enhanced glucocorticoid and no mineralocorticoid activity have been developed through appropriate chemical modifications of the glucocorticoid structure[4]. These compounds have been used extensively in the treatment of various conditions associated with excessive or persistent inflammation, such as allergies, asthma, autoimmune diseases, organ transplantation, and sepsis[5]. The impressive therapeutic efficacy of endogenous and synthetic GCs in a wide variety of disorders stems from their diverse biological actions through multiple cell signaling pathways[4,5].

BIOSYNTHESIS

The adrenal cortex produces a variety of steroid hormones, the most important being mineralocorticoids (aldosterone, desoxycorticosterone), glucocorticoids (cortisol and corticosterone), and adrenal androgens[2]. Steroid hormones are produced in distinct anatomic areas of the adrenal cortex (zona glomerulosa, fasciculata, and reticularis, respectively) from the prodromal substrate cholesterol via the action of specific oxygenases that belong to the family of cytochrome P450[6]. The response to a steroidogenic stimulus is mediated by the steroidogenic acute regulatory protein (StAR), which under the influence of ACTH enhances cholesterol transport into the mitochondria via specific receptors[6]. The scheme of adrenal steroidogenesis was delineated by analysis of the steroidogenic enzymes involved; these enzymes exert their effects on the main structural molecule, cyclopentanoperhydrophenanthrene, which consists of three cyclohexane rings and a single cyclopentane ring[6].

Cortisol biosynthesis is a multistep process preceded by the formation of several prodromal compounds under the catalytic effect of specific steroidogenic enzymes. Because of the enzymatic differences between the outer (glomerulosa) and the two inner (fasciculata and reticularis) zones of the adrenal cortex, the gland functions as two separate units, with the zonae fasciculata and reticularis possessing all the necessary enzymes for cortisol biosynthesis under ACTH regulation and the zona glomerulosa producing aldosterone. ACTH in turn is regulated by hypothalamic CRH and AVP and by higher centers in the CNS influencing the secretion of these releasing factors[7]. The delivery of ACTH to the adrenal cortex leads to the rapid synthesis and secretion of GCs, with the plasma levels of these compounds rising within minutes following ACTH administration. Other hormones, including the catecholamines (Cas), neuropeptide Y (NPY), and CRH are produced by the adrenal medulla, while there is autonomic neural input to the adrenal cortex also participating in the regulation of GC secretion[5].

Alterations in the structure of the GCs have allowed for the development of a synthetic compound with greater glucocorticoid and negligible mineralocorticoid activity. The increased activity of these compounds is due to increased affinity for the glucocorticoid receptor (GR), increased nuclear retention of this receptor, and/or decreased metabolic clearance, all mechanisms that increase overall tissue exposure to the hormone[4] (Table 1).

Table 1
Glucocorticoid, Mineralocorticoid Potency and Effect on HPA-Axis Suppression of Commonly Used Synthetic Steroids

Steroid	Anti-inflammatory action	HPA*-axis suppression	Salt retention
Cortisol	1	1	1
Prednisolone	3	4	0.75
Methylprednisolone	6.2	4	0.5
Fludrocortisone	12	12	125
Dexamethasone	26	17	0

** HPA: Hypothalamic-pituitary-adrenal*

NEUROENDOCRINE REGULATION OF GLUCOCORTICOID SECRETION

Cortisol secretion is closely regulated by ACTH, with plasma cortisol levels being parallel to those of ACTH[3,5,8]. Hypothalamic CRH and AVP secretory episodes within the hypophyseal portal system induce ACTH secretory episodes in the systemic circulation, which then stimulate cortisol secretory pulses. Because of the relatively long plasma half-life of cortisol (60-90 minutes), a circadian pattern of secretion is generated in the blood with some visible superimposed bursts. Other hormones and cytokines, as well as neural input from the autonomic nerves to the adrenal cortex, may also participate in the central regulation of cortisol secretion[3,5,8].

Cortisol secretion is low in the late evening; it gradually declines further and becomes undetectable in the first hours of sleep. Cortisol increases markedly during the early morning hours, and this increment accounts for approximately half of daily cortisol production; then it gradually declines during the day with fewer secretory episodes of decreased magnitude[2,5,7]. Although this secretory pattern is consistent, there is considerable intra- and interindividual variability and this circadian rhythm of cortisol secretion can be altered by changes in sleeping pattern, light-dark exposure, and

meal times[2,5,7]. ACTH and cortisol secretion increase in response to physical or emotional stressors, such as major illness, surgery, or trauma[4]. In the presence of stressors, plasma ACTH and cortisol are secreted within minutes; when the stress state is prolonged, circadian periodicity may be abolished, expressed as flattening of the circadian wave. HPA axis responses originate in the CNS, characterized by increased hypothalamic CRH and AVP production[2,8].

GCs along with the Cas (norepinephrine and epinephrine) are the main peripheral effectors of the stress system; adequate responsiveness of the stress system to stressors is responsible for attaining homeostasis and achieving a sense of well-being[2,7,8]. The adaptive or stress response depends not only on the intensity of the stressor but also on the inherent ability of the stress system to achieve and maintain an appropriate level and duration of activity. This implies that the stress response is terminated with the cessation of any noxious stimulus[5].

GCs play an important role in the regulation of the basal activity of the HPA axis, as well as in the termination of the stress response, by exerting negative feedback at extrahypothalamic centers, the hypothalamus, and the pituitary gland[8]. The negative feedback of GCs on CRH and ACTH secretion serves to limit the duration of the total tissue exposure of the organism to GCs, thus minimizing the catabolic, antireproductive, and immunosuppressive effects of these hormones[5]. GC feedback inhibition has both a fast component, which is transient and probably mediated by actions on the cell membranes, and a delayed component through the classic GR system. The latter suppresses the HPA-axis by mechanisms that are both time- and dose-dependent; as a consequence, the chronically suppressed HPA axis may fail to respond to stress[8].

GLUCOCORTICOID CIRCULATION AND METABOLISM

The plasma half-life of cortisol is between 60 and 90 minutes and is determined by the extent of plasma binding to specific plasma proteins and by the rate of metabolic inactivation. Following secretion in the unbound state and upon entering the circulation, cortisol binds to plasma proteins, mainly to corticosteroid-binding protein (CBG) with high affinity, and to a lesser extent to albumin with much lower affinity[9]. Bound steroids are biologically inactive and only the unbound fraction is active[9]. In basal conditions, about 10% of circulating cortisol is free, about 75% is bound to CBG,

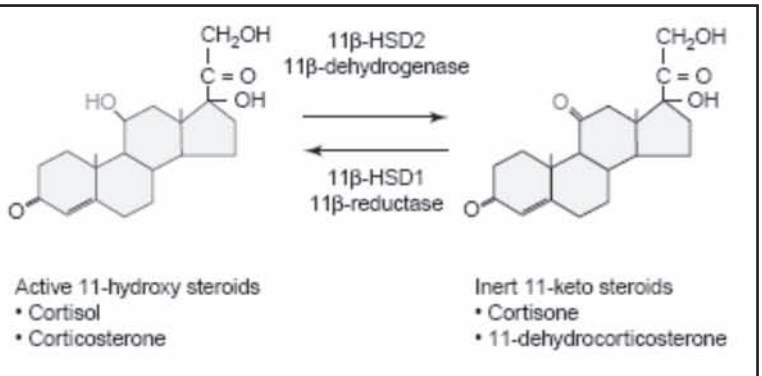

Figure 1. 11β-Hydroxysteroid dehydrogenase (11β-HSD): the glucocorticoid 'shuttle'. 11β-HSD catalyses the interconversion of active 11-hydroxy-glucocorticoids (cortisol and corticosterone) and their respective inert 11-keto forms (cortisone and 11-dehydrocorticosterone). There are two isozymes, which are the products of distinct genes. 11β-HSD2 is an nicotinamide adenine dinucleotide (NAD)-dependent dehydrogenase that exclusively catalyses the inactivation of physiological glucocorticoids. By contrast, 11β-HSD1, which is an NADP(H)-dependent bidirectional enzyme in tissue homogenates, functions predominantly as an 11-ketoreductase in intact cells and organs and *in vivo*; this reaction direction regenerates active glucocorticoids in cells producing the isozyme.

Figure 1. *Enzymatic Glucocorticoid Shuttling*

and the remainder is bound to albumin; only the biologically active free cortisol is under tight ACTH regulation and exerts its activity by binding to the GR[4]. Synthetic steroids, with the exception of prednisolone, do not bind significantly to CBG but mainly circulate bound to albumin.

GCs are metabolized in the liver by a number of metabolic conversions, the most important being the reduction of specific double bonds of the A ring of the steroid molecule. Cortisol is also converted extensively by the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD type 2) to the biologically inactive cortisone[4]. This inactivation is particularly important in the kidneys as it protects the mineralocorticoid receptor from occupancy by cortisol, and this prevents cortisol from causing a mineralocorticoid excess state[1]. Conversely, 11β-HSD type 1 converts inactive cortisone into cortisol. Over 95% of cortisol and cortisone metabolites are conjugated (mainly with glucuronic acid) by the liver and are then excreted by the kidney[10] (Figure 1).

THE GLUCOCORTICOID RECEPTOR

At the cellular level, the majority of GC effects are mediated by an approximately 94 kDa intracellular protein, the GR, which, along with other steroid hormone receptors, belongs to the superfamily of nuclear receptors[1] (Figure 2). The human GR gene is in a single locus of chromosome 5q31-32, but variation in the structure and expression of the gene generates diversity in GC signaling[11]. Human GR messenger RNA (mRNA) has at least two alternative splice variants[11]; whereas exons 2 through 8 are constant components of GR mRNA, there are two exon 9 isoforms that can be spliced to produce mature mRNA[4]. Splicing on exon 9α produces GRα mRNA, which is translated into a protein with a unique sequence of 50 amino acids at its carboxy end (Figure 2). The GRα isoform binds cortisol, DNA, and other transcription factors, thereby modifying the transcriptional activity of target genes. Limited evidence suggests that GRα may also act through nongenomic pathways; splicing of exon 9β produces GRβ mRNA[4] (Figure 2). Although GRβ protein binds DNA, it has no known binding ligand and fails to activate transcription. GRβ can also form heterodimers with GRα and interfere with the function of this protein. The relative levels of GRα and β influence cell sensitivity to GCs, with higher levels of GRβ leading to glucocorticoid resistance[12,13].

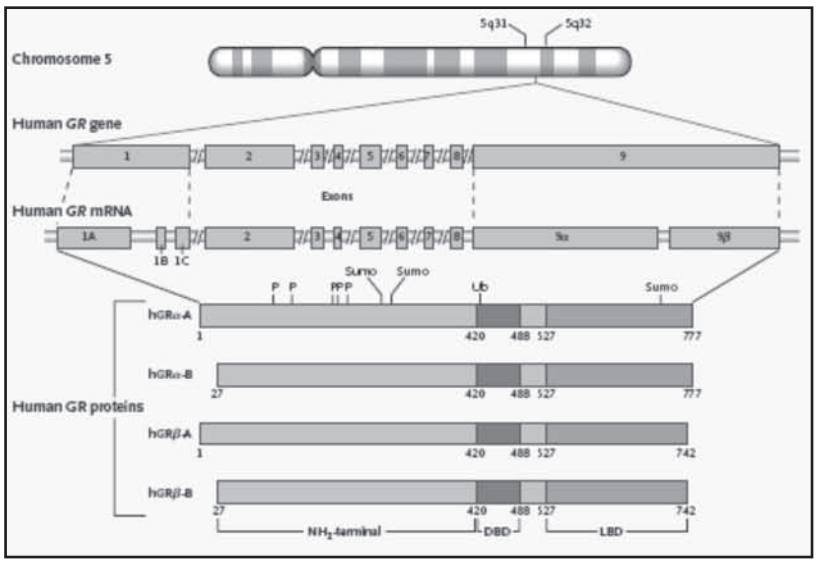

Figure 2. *Genomic Organization and Localization of the Glucocorticoid Receptor[4]*

GR-Mediated Transcriptional Regulation and Activation

GCs, being lipophilic substances, cross the cell membrane and interact with the GR; after binding of the ligand, the bound GR dissociates from the heat shock proteins (hsp) complex; within the

cell cortisol can act in several ways[4,14].. Many effects of GCs are achieved by inhibition rather than activation of target genes[8,15]. This is especially true for the anti-inflammatory/ immunosuppressive effects of GCs that involve suppressed transcription of immune genes; these genes are regulated by activated protein-1 (AP-1), a transcription factor composed of dimmers of Jun and Fos family of proteins[1]. It is thought that GR inhibits AP-1 in the absence of DNA binding, possibly via protein/ protein interaction[16]. Besides AP-1, other transcriptional factors, such as nuclear factor k-B (NF-kB) are also modulated by GCs[17]. These latter actions seem to occur at lower cortisol levels than the cortisol-glucocorticoid receptor-glucocorticoid response element complex needs to change transcription[4]. Another mechanism of action is GC signaling through membrane-associated receptors and second messengers (so-called nongenomic pathways)[18]. The most significant example is that of GC-induced fast feedback inhibition of ACTH release; this effect occurs within minutes of GC administration, and its rapidity of action suggests that it is not mediated by RNA and protein synthesis. Although the steroid-binding domain of the GR confers specificity for GC binding, GCs bind with equal affinity to aldosterone or mineralocorticoid receptors; the specificity of the GR is maintained by the expression of 11β-HSD, which converts cortisol to cortisone, and protecting the mineralocorticoid receptor from excessive GC activity (Figure 1). The study of GRs has led to the development of synthetic GCs (prednisolone, dexamethasone), which exert substantially higher affinity for the GR than cortisol when present in equimolar concentrations[10].

BIOLOGICAL EFFECTS OF GLUCOCORTICOIDS

Although GCs were originally named because of their effect on glucose metabolism, they are currently defined as steroids that exert their effects after binding to specific GRs, which mediate their actions[1,3]. These receptors are expressed in virtually all tissues, and therefore GCs exert a broad spectrum of biological effects almost throughout the body. It has been estimated that approximately 20% of the human genome is affected by GCs being either down- or up-regulated by them[5] (Figure 3). GCs in general inhibit DNA synthesis, and in many tissues they also inhibit RNA and protein synthesis, while they accelerate protein catabolism (Table 2). These actions provide substrate for intermediary metabolism. Accelerated metabolism accounts for the deleterious effects of GCs in several tissues[8,15].

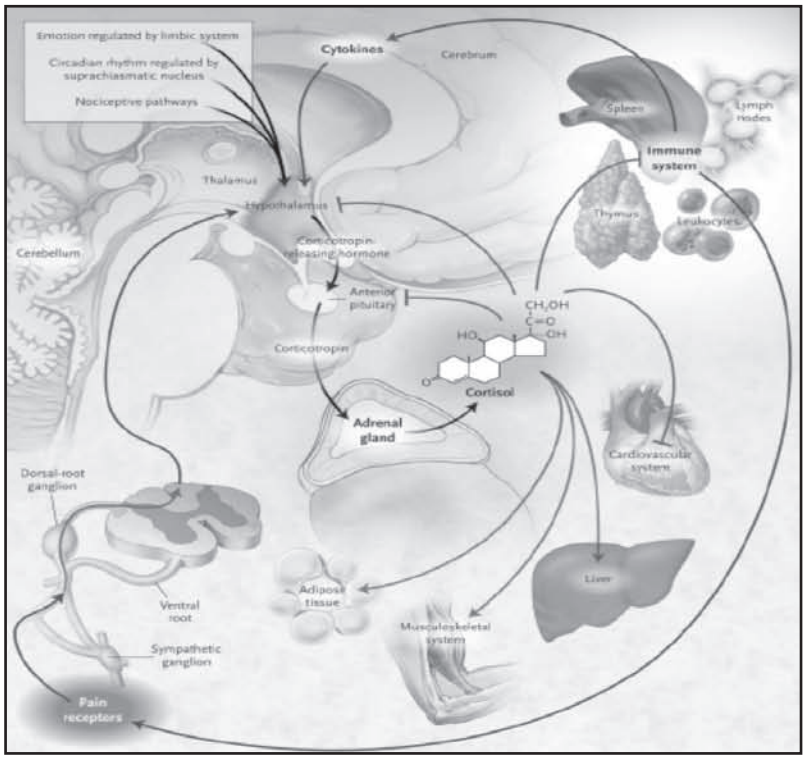

Figure 3. *Neuroendocrine Control and Diversity of Action of Glucocorticoids*[4]

Table 2
Principal Actions of Glucocorticoids in Humans: Some Consequences of Glucocorticoid Excess

System/Organ	Effect
Brain/CNS	Depression
	Psychosis
Eye	Glaucoma
Endocrine System	Reduction of LH, FSH release
	Reduction of TSH release
	Reduction of GH secretion
	Increase of appetite
Gastrointestinal tract	Increase in acid secretion
	(peptic ulceration)
Carbohydrate/Lipid metabolism	Increased hepatic glycogen deposition
	Increased peripheral insulin secretion
	Increased gluconeogenesis
	Increased fatty acid production
	Overall diabetogenic effect
	Promotion of visceral obesity
Cardiovascular/Renal	Salt and water retention
	Hypertension
Skin/muscle/Renal	Protein catabolism/collagen breakdown
	Thinning of the skin
	Muscular atrophy
Bone	Reduction of bone formation
	Reduction of bone mass
	and development of osteoporosis
Growth and development	Reduction of linear growth
Immune system	Anti-inflammatory action
	Immunosuppression

CNS, central nervous system; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone

Effects on Intermediary Metabolism

GCs increase blood glucose concentrations through their action on glycogen, protein, and lipid metabolism. These effects are minimal during the fed state, but during fasting GCs facilitate maintenance of adequate glucose concentrations. In the liver, GCs stimulate glycogen deposition and activate hepatic glucose production through the activation of key enzymes involved in gluconeogenesis[19]. In peripheral tissues, muscle, and fat, GCs inhibit glucose uptake and utilization; in adipose tissue, GCs induce lipolysis, resulting in the release of free fatty acids in the circulation[7]. GCs also have permissive effects in the action of other hormones, including catecholamines and glucagon. The net effect of GC action on intermediary metabolism is to cause insulin resistance and an increase in blood glucose concentration at the expense of muscle and lipid catabolism. GCs also stimulate adipocyte

differentiation and the development of visceral obesity in states of excessive GC production; this may be explained by the increased expression of GR and 11β-HSD type 1 in omental compared to subcutaneous adipose tissue[20,21].

Effects on Skin, Muscle, Connective Tissue, and Bone

In addition to inducing insulin resistance in muscles, GCs initiate catabolic changes in skin, muscle, and connective tissue. In muscles, GCs cause atrophy and reduce protein synthesis, whereas in skin and connective tissue they inhibit epidermal cell division, DNA synthesis, and collagen synthesis and production[8]. GCs decrease the function of osteoblasts and induce a state of an overall negative calcium balance by inhibiting intestinal calcium absorption and promoting urinary calcium excretion; serum calcium levels are maintained at the expense of net bone resorption[5]. Decreased bone formation and increased resorption are associated with osteopenia and osteoporosis, a common finding in states of excessive GC levels[5].

Effects on Cardiovascular and Renal Function and Water Homeostasis

GCs may increase cardiac output, and they also increase peripheral vascular tone by augmenting the effects on other vasoconstrictors, such as the catecholamines and angiotensin II, while reducing nitric oxide mediated endothelial dilatation[22]. Thus, shock refractory to vasoconstrictors may develop when glucocorticoid-deficient individuals are subjected to stress. In the kidney, depending on the activity of the type 2 isoenzyme of 11β-HSD, cortisol can act on the distal nephron causing sodium preservation and potassium loss[10]. Elsewhere within the nephron GCs increase glomerular filtration rate, sodium reabsorption, and free water clearance[10]. The latter effect involves antagonism of the action of vasopressin and explains the dilutional hyponatremia seen in patients with GC insufficiency.

Effects on the CNS and Gastrointestinal System

Both GC and mineralocorticoid receptors are expressed in distinct areas of the brain, and alterations of GC levels have been associated with specific psychiatric conditions[23]. GCs cause neuronal death, particularly in the hippocampus, and this may result in deficits in cognitive function, memory, behavior, and the development of neurodegenerative diseases[23]. The GR is expressed throughout the gut and the mineralocorticoid receptor is expressed at the distal colon, and they mediate the corticosteroid control of epithelial ion transport[24].

Endocrine Effects

GCs exert a permissive effect in growth and development by accelerating the development of several tissues in fetal life, probably through interaction with various growth factors. This is demonstrated by the increased surfactant production in fetal lung and the accelerated development of hepatic and gastrointestinal enzyme systems[25]. However, elevated GC levels suppress pituitary growth hormone (GH) secretion and induce resistance to the action of GH and insulin growth factor (IGF) 1[5]. GCs suppress the thyroid axis, probably through a direct action on thyroid-stimulating hormone (TSH) secretion. In addition, they inhibit 5' deiodinase activity that mediates the conversion of thyroxine to active triiodothyronine (T_3). During inflammatory stress, inflammatory cytokines, such as tumor necrosis factor α (TNF-α, interleukin (IL)-1, and IL-6, also activate CRH secretion and inhibit 5' deiodinase activity, resulting in decreased T_3 and increased reverse T_3 levels[7,8]. GCs also act centrally at the hypothalamic level to inhibit the pulsatile secretion of gonadotropin-releasing hormone (GnRH)

by GnRH neurons and thus luteinizing hormone and follicle-stimulating hormone release; GCs also render target tissues of gonadal steroids resistant to these hormones[7]. These inhibitory effects on the major anabolic hormones and the potential preferential tissue-specific expression of 11β-HSD may account for the development of omental obesity in states of excessive GC secretion[7].

Effects on the Immune System

GCs influence the traffic of circulating leukocytes and inhibit many functions of leukocytes and immune accessory cells. They suppress the immune activation of these cells, inhibit the production of proinflammatory cytokines and other mediators of inflammation, and cause proinflammatory cytokine resistance. Furthermore, GCs influence the secretion rates of specific proteins and alter the electrical potential of neuronal cells through mechanisms that remain to be elucidated. Cytokines can also act directly on the brain to activate the HPA-axis[4] (Figure 4).

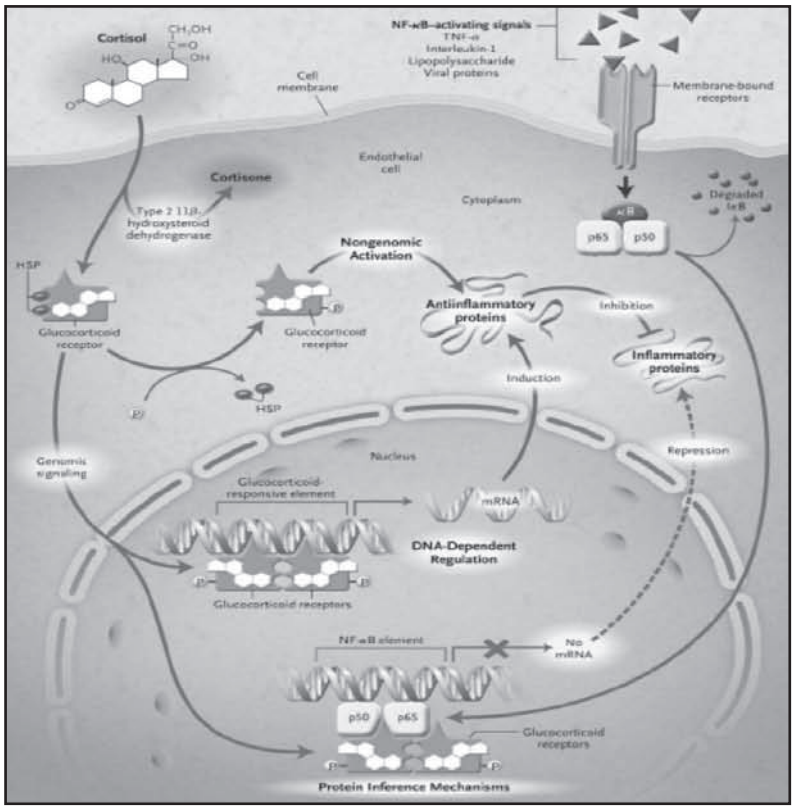

Figure 4. *Glucocorticoid (Cortisol) Mechanism of Action and its Effect on the Immune System*

GLUCOCORTICOIDS AND THE STRESS RESPONSE

The stress response is subserved by the stress system, which is located both in the CNS and the periphery. The principal effectors of the stress system include the CRH, AVP, the proopiomelanocortin (POMC)-derived peptides α-melanocyte-stimulating hormone (MSH) and β-endorphin, the GCs, and the Cas[2,8]. Activation of the central CRH and locus ceruleus-norepinephrine (LC-NE) systems leads to subsequent secretion of large amounts of GCs and Cas[5]. As a consequence, cardiac output and respiration are enhanced and blood flow is redirected to provide the highest perfusion to the brain and musculoskeletal system[7] (Figure 3). Endocrine programs of growth and reproduction are suppressed in order to save energy; catabolism is enhanced and fuel is used to supply the brain, heart, and muscles, accompanied by increases in glucose levels, heart rate, and blood pressure[7]. In addition, stress induces a state of immunomodulation, particularly inhibiting innate and cellular immunity and

favouring humoral immunity. All these adaptations are protective and help to maintain homeostasis in the short term but can be damaging in the long term if the mediators are chronically overproduced, underproduced, or dysregulated[23]. This new understanding helps to explain some well known, but often contradictory, effects of stress on a variety of infectious, autoimmune/inflammatory, allergic, metabolic, adaptive, and neoplastic diseases.

CLINICAL ASPECTS OF TREATMENT WITH GLUCOCORTIOCIDS

Chronic GC therapy is used for the treatment of a variety of autoimmune and inflammatory disorders, mostly for its potent anti-inflammatory and immunosuppressive effects. Once the therapeutic goal has been achieved and to avoid, to the extent possible, steroid-induced side effects, including chronic suppression of the HPA axis, early tapering and/or complete discontinuation of GC treatment is recommended. Abrupt cessation and/or rapid withdrawal of GCs in such patients may cause symptoms of adrenal insufficiency. Occasionally, psychologic dependence on GCs may develop. The potency, dose, and duration of GC administration are important albeit imperfect predictors of HPA axis suppression.

Patients who are likely to have HPA axis suppression are usually those who also develop a Cushingoid habitus, have received a GC dose equivalent to ≥20 mg of prednisone per day for longer than 2 weeks, and/or have received mostly bedtime doses of GCs. Such patients do not require testing to evaluate HPA axis function but should be dealt with as patients with secondary adrenal insufficiency. They should be given standard instructions, including wearing a medical alert bracelet and carrying injectable GCs for use in case of an emergency. Suppression of the HPA axis is less likely in those who have received any dose of GCs for <2 weeks and/or have been treated with alternate day GC therapy using short- or intermediate-acting synthetic GCs. If withdrawal from GCs is desired, gradual reduction of the dose of GC is performed; such patients do not need to be tested for HPA axis reserve unless abrupt discontinuation is required. In such an event the response to the administration of synthetic ACTH is the preferred method. Although the ACTH test does not provide direct information about the hypothalamic function of the patient, it is an easy test that can be performed on an outpatient basis. The standard high-dose ACTH test (250 μg) is usually used for this purpose. A baseline venous blood sample for cortisol estimation prior to ACTH administration is taken and then 250 μg of ACTH is administered either intravenously or intramuscularly; venous blood is obtained 30 and 60 minutes after ACTH administration and serum cortisol is measured at these time points. A serum cortisol value of ≥18 μg/dL is indicative of intact HPA axis function.

Short-term GC therapy (up to 2 weeks), even at high doses, requires no tapering and can be stopped abruptly, as HPA axis suppression is highly unlikely and, even if present, is of small clinical significance. In patients who have received treatment with GCs for longer periods, tapering may be necessary, as in patients who have received prolonged treatment with prednisone in excess of 5 mg daily (at this dose, HPA axis suppression is highly unlikely). Interestingly, administration of very high doses of GCs to patients in high stress conditions, such as hematological cancer patients receiving high doses of prednisone or prednisolone, does not cause adrenal suppression.

Tapering should be performed according to the following paradigm:

- 10 mg/day dose reduction every 1 to 2 weeks from an initial dose of GCs above 60 mg of prednisone per day (see Table 1 to compare the anti-inflammatory action and effect on HPA axis suppression between different synthetic steroids)
- 5 mg/day dose reduction every 1 to 2 weeks when doses of GCs equivalent to 20 to 60 mg of prednisone per day have been used

- 2.5 mg/day dose reduction every 1 to 2 weeks when doses of GCs equivalent to 10 to 20 mg of prednisone per day have been used
- 1 mg/day dose reduction every 1 to 2 weeks when doses of GCs equivalent to 6 to 10 mg of prednisone per day have been used

This regimen is usually not associated with symptoms of cortisol deficiency, although it may be difficult to distinguish such symptoms from those of disease recurrence. In this setting, small increments of the dose of prednisone and careful monitoring of the patient for 2 to 4 weeks may be required (see also assessment of HPA axis suppression). When symptoms resolve, tapering according to the regimen above could be reintroduced. When this modest increase of GCs is not sufficient to alleviate symptoms, doubling of the dose at which symptoms occurred and maintenance of this dose for 2 to 3 weeks usually suffices to alleviate symptoms. If symptoms resolve, the previous tapering regimen can be resumed using 2- to 4-week rather 1- to 2-week intervals between decrements. Although data regarding tapering in patients using alternate-day regimens are sparse, similar reductions of GCs are employed, decreasing the alternate-day dose by 5 to 10 mg every 1 to 2 weeks. Rarely, when symptoms suggestive of an adrenal crisis develop, therapy should be introduced immediately, without awaiting biochemical confirmation. Following adequate fluid and electrolyte replacement, hydrocortisone is used (50-100 mg intravenously every 6-8 hours). When such doses of hydrocortisone are employed concomitant mineralocorticoid replacement is not necessary, as hydrocortisone exerts an adequate mineralocorticoid effect.

CONCLUSION

GCs are an integral part of the peripheral limb of the stress system, which coordinates the adaptive response of the organism to stressors and plays an important role in the maintenance of basal and stress-related homeostasis. They are pleiotropic hormones affecting a wide range of tissues and inducing a variety of behavioral and physical changes that improve the ability of the organism to adapt and increase its chances for survival. However, a quantitatively or temporally inadequate or excessive response to stressors may result in a variety of endocrine, metabolic, autoimmune, and psychiatric disorders.

REFERENCES

1. Bamberger CM, Schulte HM, Chrousos GP. Molecular determinants of glucocorticoid receptor function and tissue sensitivity to glucocorticoids. Endocr Rev. 1996;17:245-261.
2. Chrousos GP. Regulation and dysregulation of the hypothalamic-pituitary-adrenal axis. The corticotropin-releasing hormone perspective. Endocrinol Metab Clin North Am. 1992;21:833-858.
3. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332:1351-1362.
4. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. N Engl J Med. 2005;353:1711-1723.
5. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol. 2005;67:259-284.
6. Borkowski AJ, Levin S, Delcroix C, Mahler A, Verhas V. Blood cholesterol and hydrocortisone production in man: quantitative aspects of the utilization of circulating cholesterol by the adrenals at rest and under adrenocorticotropin stimulation. J Clin Invest. 1967;46:797-811.

7. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53:865-871.
8. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA. 1992;267:1244-1252.
9. Breuner CW, Orchinik M. Plasma binding proteins as mediators of corticosteroid action in vertebrates. J Endocrinol. 2002;175:99-112.
10. Stewart PM, Krozowski ZS. 11 beta-Hydroxysteroid dehydrogenase. Vitam Horm. 1999;57:249-324.
11. Lu NZ, Cidlowski JA. The origin and functions of multiple human glucocorticoid receptor isoforms. Ann N Y Acad Sci. 2004;1024:102-123.
12. Pujols L, Mullol J, Perez M, Roca-Ferrer J, Juan M, Xaubet A, Cidlowski JA, Picado C. Expression of the human glucocorticoid receptor alpha and beta isoforms in human respiratory epithelial cells and their regulation by dexamethasone. Am J Respir Cell Mol Biol. 2001;24:49-57.
13. Yudt MR, Cidlowski JA. Molecular identification and characterization of a and b forms of the glucocorticoid receptor. Mol Endocrinol. 2001;15:1093-1103.
14. Hebbar PB, Archer TK. Chromatin remodeling by nuclear receptors. Chromosoma. 2003;111:495-504.
15. Papanicolaou DA, Chrousos GP. Interactions of the endocrine and immune systems in children and young adults. Curr Opin Pediatr. 1995;7:440-444.
16. Schule R, Rangarajan P, Kliewer S, Ransone LJ, Bolado J, Yang N, Verma IM, Evans RM. Functional antagonism between oncoprotein c-Jun and the glucocorticoid receptor. Cell. 1990;62:1217-1226.
17. Auphan N, DiDonato JA, Rosette C, Helmberg A, Karin M. Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. Science. 1995;270:286-290.
18. Hafezi-Moghadam A, Simoncini T, Yang Z, et al. Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase. Nat Med. 2002;8:473-479.
19. Magnuson MA, Quinn PG, Granner DK. Multihormonal regulation of phosphoenolpyruvate carboxykinase-chloramphenicol acetyltransferase fusion genes. Insulin's effects oppose those of cAMP and dexamethasone. J Biol Chem. 1987;262:14917-14920.
20. Bronnegard M, Arner P, Hellstrom L, Akner G, Gustafsson JA. Glucocorticoid receptor messenger ribonucleic acid in different regions of human adipose tissue. Endocrinology. 1990;127:1689-1696.
21. Bujalska IJ, Kumar S, Stewart PM. Does central obesity reflect "Cushing's disease of the omentum"?. Lancet. 1997;349:1210-1213.
22. Grunfeld JP, Eloy L. Glucocorticoids modulate vascular reactivity in the rat. Hypertension. 1987;10:608-618.
23. McEwen BS, De Kloet ER, Rostene W. Adrenal steroid receptors and actions in the nervous system. Physiol Rev. 1986;66:1121-1188.
24. Pressley L, Funder JW. Glucocorticoid and mineralocorticoid receptors in gut mucosa. Endocrinology. 1975;97:588-596.
25. Iannuzzi DM, Ertsey R, Ballard PL. Biphasic glucocorticoid regulation of pulmonary SP-A: characterization of inhibitory process. Am J Physiol 1993;264(3 Pt 1):L236-L244.