**GLUCOCORTICOIDS. The thyroid.**

The pituitary gland and the adrenal cortex release hormones that regulate salt and water balance, energy expenditure, growth, sexual behaviour, immune function and many other vital mechanisms. The commander-in-chief of this impressive hormonal campaign is the hypothalamus and the functioning unit is known as the hypothalamo–pituitary–adrenal (HPA) axis.

The adrenal glands consist of two parts: the inner medulla, which secretes catecholamines and the outer cortex, which secretes adrenal steroids. The cortex comprises three concentric zones: the zona glomerulosa (the outermost layer), which elaborates mineralocorticoids, the zona fasciculata, which elaborates glucocorticoids, and the innermost zona reticularis, which produces androgen precursors. The principal adrenal steroids are those with glucocorticoid and mineralocorticoid activities.

The mineralocorticoids regulate water and electrolyte balance, and the main endogenous hormone is aldosterone. The glucocorticoids have widespread actions on carbohydrate and protein metabolism, as well as potent regulatory effects on host defence mechanisms. The adrenal gland secretes a mixture of glucocorticoids; in humans the main hormone is hydrocortisone (also, confusingly, known as cortisol), and in rodents it is corticosterone. The mineralocorticoid and glucocorticoid actions are not completely separated in naturally occurring steroids and some glucocorticoids have quite substantial effects on water and electrolyte balance. In fact, both hydrocortisone and aldosterone are equiactive on mineralocorticoid receptors but, in mineralocorticoid-sensitive tissues such as the kidney, the action of 11β-hydroxysteroid dehydrogenase Type 2 converts hydrocortisone to the inactive metabolite cortisone,5 thereby preventing the tissue from responding to hydrocortisone. Interestingly, there is increasing evidence that some glucocorticoid synthesis can take place locally at extra-adrenasites such as thymus and skin (see Talaber et al., 2015; Hannen et al., 2017) providing a fresh perspective on the local control of inflammatory processes. With the exception of replacement therapy, glucocorticoids are most commonly employed for their anti-inflammatory and immunosuppressive properties. In this therapeutic context, their metabolic and other actions are seen as unwanted side effects. Synthetic steroids have been developed in which exhibit a partial separation of the glucocorticoid from the mineralocorticoid actions, but it has not yet been possible completely to separate the anti-inflammatory from the other actions of the glucocorticoids.

GLUCOCORTICOIDS

Synthesis and release Glucocorticoids are not stored in the adrenal gland but are synthesised under the influence of circulating ACTH secreted from the anterior pituitary gland and released in a pulsatile fashion into the blood. While glucocorticoids are continuously released, there is a welldefined circadian rhythm in the secretion in healthy humans, with the net blood concentration being highest early in the morning, gradually diminishing throughout the day and reaching a low point in the evening or night. ACTH secretion itself (also pulsatile in nature) is regulated by CRF released from the hypothalamus, and by vasopressin released from the posterior pituitary gland. The release of both ACTH and CRF, in turn, is reflexly inhibited by the ensuing rising concentrations of glucocorticoids in the blood. Opioid peptides also exercise a tonic inhibitory control on the secretion of CRF, and psychological factors excessive heat or cold, injury or infections can also affect the release of both vasopressin and CRF. This is the principal mechanism whereby the HPA axis is activated in response to perceived threats in the external environment. The biosynthetic precursor of glucocorticoids is cholesterol. The initial conversion of cholesterol to pregnenolone is the rate-limiting step and is regulated by ACTH. Some biosynthetic reactions can be inhibited by drugs and these have a utility in treating Cushing’s disease or adrenocortical carcinoma. Metyrapone prevents the β-hydroxylation at C11, and thus the formation of hydrocortisone and corticosterone. Synthesis is blocked at the 11-deoxycorticosteroid stage, leaving intermediates that have no effects on the hypothalamus and pituitary so there is a marked increase in ACTH in the blood. Metyrapone can therefore be used to test ACTH production and may also be used to treat patients with Cushing’s syndrome. Trilostane (previously used to treat Cushing’s syndrome and primary hyperaldosteronism but now largely restricted to veterinary indications) blocks an earlier enzyme in the pathway – the 3β-dehydrogenase. Aminoglutethimide inhibits the initial step in the biosynthetic pathway and has the same overall effect as metyrapone. Trilostane and aminoglutethimide are not currently used in the United Kingdom but ketoconazole, an antifungal agent , also inhibits steroidogenesis and may be of value in the specialised treatment of Cushing’s syndrome. Mitotane suppresses glucocorticoid synthesis by a direct (and unknown) mechanism on the adrenal

**Mechanism of glucocorticoid action**

The glucocorticoid effects relevant to this discussion are initiated by interaction of the drugs with specific intracellular glucocorticoid receptors6 belonging to the nuclear receptorsuperfamily (although there may be other binding proteins or sites; see Norman et al., 2004). This superfamily also includes the receptors for mineralocorticoids, the sex steroids, thyroid hormones, vitamin D3 and retinoic acid. The actual mechanism of transcriptional control is complex, with at least four mechanisms operating within the nucleus. These are summarised diagrammatically in Fig. 34.6. When the nuclear actions of glucocorticoid receptors were first discovered it was thought that this mechanism could account for all the actions of the hormones, but a surprising discovery overturned this idea. Reichardt et al. (1998), using transgenic mice in which the glucocorticoid receptor was unable to dimerise (and therefore unable to function in the nucleus), found that glucocorticoids were still able to exert a great many biological actions. This suggested that in addition to controlling gene expression within the nucleus, the liganded receptor itself could initiate important signal transduction events while still in the cytosolic compartment (there may even be a subpopulation of receptors that reside there permanently). One such effect seems to be interaction of the receptor with the regulatory complex, NF-κB and other important interactions may involve protein kinases/phosphatase signalling systems. Some of these cytosolic actions are very rapid. For example, the liganded glucocorticoid receptor-induced phosphorylation by PKC and subsequent release of the protein annexin A1, which has potent inhibitory effects on leukocyte trafficking and other anti-inflammatory actions, occurs in minutes and cannot be accounted for by changes in protein synthesis and there are many other examples. In recent years, our understanding of the glucocorticoid field has been further enriched by the discovery of numerous isoforms and splice variants of glucocorticoid receptor (GR), some of which are expressed in a tissue-specific manner. This opens up a real possibility of highly selective glucocorticoid drugs in the future.

**Mechanism of action of the glucocorticoids**

• Glucocorticoids bind intracellular receptors that then dimerise, migrate to the nucleus and interact with DNA to modify gene transcription, inducing synthesis of some proteins and inhibiting synthesis of others.

• Many acute glucocorticoid actions are mediated by signalling systems triggered by the liganded receptor in the cytosol. Some are very rapid.

• There may be different populations of receptors including membrane bound receptors which may also transduce rapid actions.

• Tissue and spice variants of the glucocorticoid receptor are found to be distributed in a tissue-specific fashion

**Actions**

General metabolic and systemic effects The main metabolic effects are on carbohydrate and protein metabolism. The glucocorticoids cause both a decrease in the uptake and utilisation of glucose and an increase in gluconeogenesis, resulting in a tendency to hyperglycaemiasee. There is a concomitant increase in glycogen storage, which may be a result of insulin secretion in response to the increase in blood sugar. Overall, there is decreased protein synthesis and increased protein break down, particularly in muscle, and this can lead to tissue wasting. Catecholamines and some other hormones cause lipase activation through a cAMP-dependent kinase, the synthesis of which requires the ‘permissive’ presence of glucocorticoids and are several other examples of this type of hormone action have been observed. Large doses of glucocorticoids given over a long period result in theredistribution of body fat characteristic of Cushing’s syndrome. Glucocorticoids tend to produce a negative calcium balance by decreasing Ca2+ absorption in the GI tract and increasing its excretion by the kidney. Together with increased breakdown of bone matrix protein this may cause osteoporosis In higher, non-physiological concentrations, the glucocorticoids have some mineralocorticoid actions, causing Na+ retention and K+ loss – possibly by swamping the protective 11β-hydroxysteroid dehydrogenase and acting at mineralocorticoid receptors Negative feedback effects on the anterior pituitary and hypothalamus Both endogenous and exogenous glucocorticoids have a negative feedback effect on the secretion of CRF and ACTH , thus inhibiting the secretion of endogenous glucocorticoids and potentially causing atrophy of the adrenal cortex. If therapy is prolonged, it may take many months to return to normal function once the drugs are stopped. Anti-inflammatory and immunosuppressive effects Endogenous glucocorticoids maintain a low-level antiinflammatory tone, and are secreted in increased amounts in response to inflammatory stimuli. Consequently, adrenalectomised animals and humans with adrenal insufficiency show a heightened response to even mild insultand injuries. On this basis, it has been suggested that a failure of appropriate glucocorticoid secretion in response to injury or infection may underlie certain chronic inflammatory human pathologies. Exogenous glucocorticoids are the anti-inflammatory drugs par excellence, and when given therapeutically, suppress the operation of both the innate and adaptive immune system. They reverse virtually all types of inflammatory reaction, whether caused by invading pathogens, by chemical or physical stimuli, or by inappropriately deployed immune responses such as are seen in hypersensitivity or autoimmune disease. When used prophylactically to suppress graft rejection glucocorticoids are more efficient in suppressing the initiation and generation of the immune response than they are in preventing the operation of an established response where clonal proliferation has already occurred.



Given that glucocorticoids modify the expression of so many genes (approximately 1% of the total genome is affected), and that the extent and direction of regulation varies between tissues and even at different times during disease, you will not be surprised to learn that their antiinflammatory effects are complex.

Actions on inflammatory cells include:

• decreased egress of neutrophils from blood vessels and reduced activation of neutrophils, macrophages and mast cells secondary to decreased transcription of the genes for cell adhesion factors and cytokines;

• decreased overall activation of T-helper (Th) cells, reduced clonal proliferation of T cells, and a ‘switch’ from the Th1 to the Th2 immune response;

• decreased fibroblast function, less production of collagen and glycosaminoglycans, and, under some circumstances, reduced healing and repair

Endogenous anti-inflammatory glucocorticoids circulate constantly in the blood and are increased during inflammatory episodes – or even by the anticipation of a stressful event. It is suggested, that the anti-inflammatory and immunosuppressive ac ions of endogenous glucocorticoids play a crucial counter-regulatory role, in that they prevent excessive activation of inflammation and other powerful defence reactions that might, if unchecked, threaten homeostasis. Certainly, this view is borne out by experimental work. While these drugs are of great value in treating conditions characterised by hyper sensitivity and unwanted inflammation, they carry the hazard that they are able to suppress the same defence reactions that protect us from infection and other insults. Unwanted effects Low-dose glucocorticoid replacement therapy is usually without problems but serious unwanted effects occur with large doses or prolonged administration of glucocorticoids.

The major effects are as follows:

• Suppression of the response to infection or injury: opportunistic infection can be potentially very serious unless quickly treated with antimicrobial agents along with an increase in the dose of steroid. Oral thrush (candidiasis, a fungal infection; see frequently occurs when glucocorticoids are taken by inhalation, because of suppression of local anti-infective mechanisms. Wound healing is impaired, and peptic ulceration may also occur.

• Cushing’s syndrome .

• Osteoporosis, with the attendant hazard of fractures, is one of the main limitations to long-term glucocorticoid therapy. These drugs influence bone density both by regulation of calcium and phosphate metabolism and through effects on collagen turnover. They reduce osteoblast function (which deposits bone matrix) and increase the activity of osteoclasts (which digest bone matrix). An effect on the blood supply to bone can result in avascular necrosis of the head of the femur.

• Hyperglycaemia produced by exogenous glucocorticoids may develop into frank diabetes.

• Muscle wasting and proximal muscle weakness.

• In children, inhibition of growth7 if treatment is continued for more than 6 months. • CNS effects: euphoria and psychosis with short-term administration, depression with chronic treatment. Given that glucocorticoids modify the expression of so many genes (approximately 1% of the total genome is affected), and that the extent and direction of regulation varies between tissues and even at different times during disease, you will not be surprised to learn that their antiinflammatory effects are complex.

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Actions on the mediators of inflammatory and immune responses include:

• decreased production of prostanoids through reduced expression of cyclo-oxygenase II and suppression of substrate arachidonic acid release;

• decreased generation of many cytokines, including IL-1, IL-2, IL-3, IL-4, IL-5, IL 6, IL-8, TNF-α, cell adhesion factors and granulocyte–macrophage Also: Osteoporosis Tendency to hyperglycaemia Negative nitrogen balance Increased appetite Increased susceptibility to infection Obesity (Benign intracranial hypertension) (Cataracts) Moon face, with red (plethoric) cheeks Increased abdominal fat (Avascular necrosis of femoral head) Easy bruising Poor wound healing Buffalo hump (Hypertension) Thinning of skin Euphoria (though sometimes depression or psychotic symptoms, and emotional lability) Thin arms and legs: muscle wasting Fig. Cushing’s syndrome. This is caused by excessive exposure to endogenous glucocorticoids, by disease (e.g. an adrenocorticotrophic hormone-secreting tumour) or by prolonged administration of glucocorticoid drugs (iatrogenic Cushing’s syndrome). Italicised effects are particularly common. Less frequent effects, related to dose and duration of therapy, are shown in parentheses. (Redrawn from Baxter & Rousseau, 1979) 7 However, some of the diseases for which glucocorticoids are indicated themselves retard growth. In a classical trial, glucocorticoid treatment increased growth in adolescents with inflammatory bowel disease as the disease resolved (Whittington et al., 1977).

• Other effects: glaucoma (in genetically predisposed persons), raised intracranial pressure and an increased incidence of cataracts. Sudden withdrawal of the drugs after prolonged therapy may result in acute adrenal insufficiency because of suppression of the patient’s capacity to synthesise corticosteroids.8 Careful procedures for phased withdrawal should be followed. Recovery of full adrenal function usually takes about 8 weeks, although it can take 18 months or more after prolonged high-dose treatment.

**Pharmacokinetic aspects**

There are many glucocorticoid drugs in therapeutic use. Although cortisol (hydrocortisone), the endogenous hormone, is often used, synthetic derivatives are even more common. These have different physicochemical properties as well as varying potencies and have been optimised for administration by oral, systemic or intra-articular routes or for topical application such as by aerosol directly into the respiratory tract or nose or as eye drops. They may be formulated as creams or ointments for application to the skin (see Ch. 28); or as foam enemas for the GI tract (Ch. 31). Topical administration diminishes the likelihood of systemic toxic effects unless large quantities are used. When prolonged use of systemic glucocorticoids is necessary, therapy on alternate days may decrease suppression of the HPA axis and other unwanted effects. Endogenous glucocorticoids are transported in the plasma bound to corticosteroid-binding globulin (CBG) and to albumin. About 77% of plasma hydrocortisone is bound to CBG, but many synthetic glucocorticoids are not bound at all. Albumin has a lower affinity for hydrocortisone but binds both natural and synthetic steroids. Both CBG-bound and albumin-bound steroids are biologically inactive. Hydrocortisone has a plasma half-life of 90 min, although many of its biological effects have a latency of 2–8 h. As small lipophilic molecules, glucocorticoids probably enter their target cells by simple diffusion. Biological inactivation, which occurs in liver cells and elsewhere, is initiated by reduction of the C4–C5 double bond. Cortisone and prednisone are inactive until converted in vivo by the 11β dehydrogenase type 1 to hydrocortisone and prednisolone, respectively. The clinical uses of systemic glucocorticoids are summarised in the clinical box. Dexamethasone has a special use: it is used to test HPA axis function. In the dexamethasone suppression test a relatively low dose of dexamethasone is given, usually at night. This would be expected to suppress the hypothalamus and pituitary, resulting in a reduced ACTH secretion and hydrocortisone output in the plasma about 9 h later. Failure of suppression implies hypersecretion of ACTH or of glucocorticoids (Cushing’s syndrome)

**Actions of glucocorticoids**

Common drugs used systemically include hydrocortisone, prednisolone and dexamethasone. Metabolic actions

• Carbohydrates: decreased uptake and utilisation of glucose accompanied by increased gluconeogenesis; this causes a tendency to hyperglycaemia.

• Proteins: increased catabolism, reduced anabolism.

• Lipids: a permissive effect on lipolytic hormones and a redistribution of fat, as observed in Cushing’s syndrome. Regulatory actions

• Hypothalamus and anterior pituitary gland: a negative feedba k action resulting in reduced release of ACTH and therefore endogenous glucocorticoids

• Cardiovascular system: reduced vasodilatation, decreased fluid exudation.

• Musculoskeletal: decreased osteoblast and increased osteoclast activity.

• Inflammation and immunity: – in acute inflammation: decreased influx and activity of leukocytes; – in chronic inflammation: decreased activity of mononuclear cells, decreased angiogenesis, less fibrosis; – in lymphoid tissues: decreased clonal expansion of T and B cells, and decreased action of cytokine secreting T cells. Switch from Th1 to Th2 response; – decreased production and action of many pro inflammatory cytokines, including interleukins, tumour necrosis factor-α and granulocyte– macrophage colony-stimulating factor; – reduced generation of eicosanoids; – decreased generation of IgG; – decrease in complement components in the blood; – increased release of anti-inflammatory factors such as interleukin (IL)-10, IL-1ra and annexin 1.

• Overall effects: reduction in the activity of the innate and acquired immune systems, but also diminution in the protective aspects of the inflammatory response and sometimes decreased healing. 8 Patients on long-term glucocorticoid therapy are advised to carry a card stating, ‘I am a patient on

**STEROID TREATMENT** which must not be stopped abruptly’. volume and sometimes hypokalaemia, alkalosis and hypertension. Decreased secretion, as in some patients with Addison’s disease, causes Na+ loss and a marked decrease in extracellular fluid volume. There is a concomitant decrease in the excretion of K+ , resulting in hyperkalaemia. Regulation of aldosterone synthesis and release The regulation of the synthesis and release of aldosterone depends mainly on the electrolyte composition of the plasma and on the activity of the angiotensin II system. Low plasma Na+ or high plasma K+ concentrations directly stimulate aldosterone release from the zona glomerulosa cells of the adrenal. Depletion of Na+ also activates the renin–angiotensin system. One of the effects of angiotensin II is to increase the synthesis and release of aldosterone

**Pharmacokinetics and unwanted actions of the glucocorticoids**

• Administration can be oral, topical or parenteral. Most naturally occurring glucocorticoids are transported in the blood by corticosteroid-binding globulin or albumen and enter cells by diffusion. They are metabolised in the liver.

• Unwanted effects are seen mainly after prolonged systemic use as anti-inflammatory or immunosuppressive agents but not usually following replacement therapy. The most important of these are: – suppression of response to infection – suppression of endogenous glucocorticoid synthesis – metabolic actions (see earlier) – osteoporosis – iatrogenic Cushing’s syndrome

**Clinical uses of glucocorticoids**

• Replacement therapy for patients with adrenal failure (Addison’s disease).

• Anti-inflammatory/immunosuppressive therapy: – in asthma

– topically in various inflammatory conditions of skin, eye, ear or nose (e.g. eczema, allergic conjunctivitis or rhinitis;

– hypersensitivity states (e.g. severe allergic reactions)

– in miscellaneous diseases with autoimmune and inflammatory components (e.g. rheumatoid arthritis and other ‘connective tissue’ diseases, inflammatory bowel diseases, some forms of haemolytic anaemia, idiopathic thrombocytopenic purpura) – to prevent graft-versus-host disease following organ or bone marrow transplantation

• In neoplastic disease: – in combination with cytotoxic drugs in treatment of specific malignancies (e.g. Hodgkin’s disease, acute lymphocytic leukaemia) – to reduce cerebral oedema in patients with metastatic or primary brain tumours (dexamethasone).

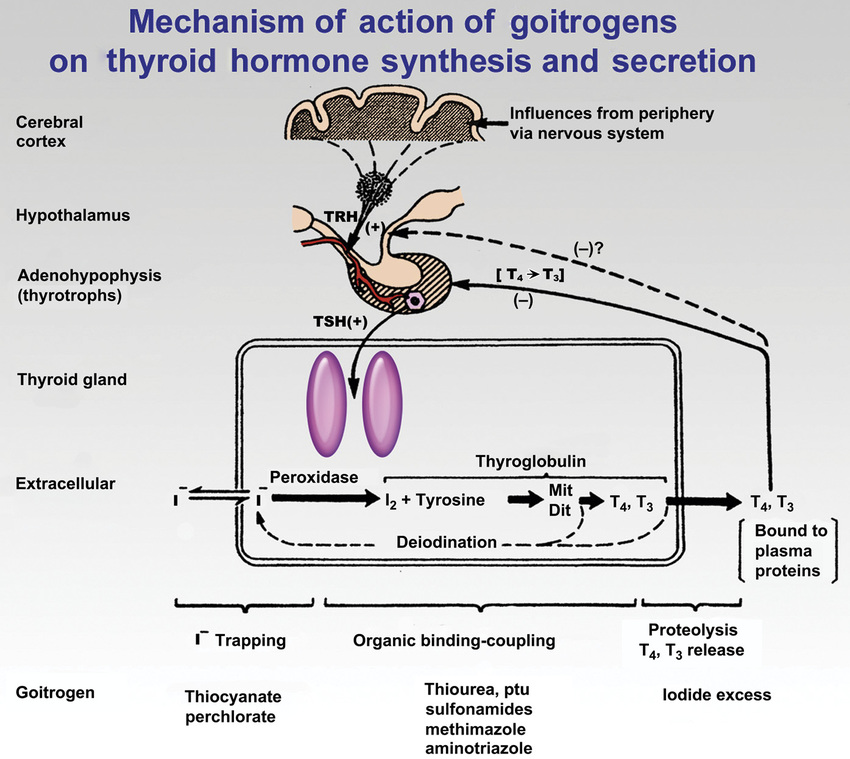
**Mineralocorticoids**

Fludrocortisone is given orally to produce a mineralocorticoid effect. This drug:

• increases Na+ reabsorption in distal tubules and increases K and H+ efflux into the tubules;

• acts on intracellular receptors that modulate DNA transcription, causing synthesis of Na+ channel and other proteins that mediate the effect of the drug;

• may be used together with a glucocorticoid in replacement therapy regimes



The thyroid

• Thyroid hormones, tri-iodothyronine (T3) and thyroxine (T4), are synthesised by iodination of tyrosine res dues on thyroglobulin within the lumen of the thyroid follicle.

• Hormone synthesis and secretion are regulated by thyroid-stimulating hormone (thyrotropin) and influenced by plasma iodide.

• There is a large pool of T4 in the body; it has a low turnover rate and is found mainly in the circulation. • There is a small pool of T3 in the body; it has a fast turnover rate and is found mainly intracellularly.

• Within target cells, the T4 is converted to T3, which interacts with a nuclear receptor to regulate gene transcription.

• T3 and T4 actions: – stimulation of metabolism, causing increased oxygen consumption and increased metabolic rate; – regulation of growth and development.

• Abnormalities of thyroid function include: – hyperthyroidism (thyrotoxicosis): either diffuse toxic goitre or toxic nodular goitre; – hypothyroidism: in adults this causes myxoedema, in infants, gross retardation of growth and mental deficiency; – simple non-toxic goitre caused by dietary iodine deficiency, usually with normal thyroid function

**Clinical use of drugs acting on the thyroid Radioiodine**

• Hyperthyroidism (Graves’ disease, multinodular toxic goitre).

• Relapse of hyperthyroidism after failed medical or surgical treatment. Carbimazole or propylthiouracil

• Hyperthyroidism (diffuse toxic goitre); at least 1 year of treatment is needed.

• Preliminary to surgery for toxic goitre.

• Part of the treatment of thyroid storm (very severe hyperthyroidism); propylthiouracil is preferred, combined with a β-adrenoceptor antagonist (e.g. propranolol). Thyroid hormones and iodine

• Levothyroxine (T4) is the standard replacement therapy for hypothyroidism.

• Liothyronine (T3), administered by slow intravenous injection, is used for myxoedema coma

• Iodine dissolved in aqueous potassium iodide (‘Lugol iodine’) is used short term to control thyrotoxicosis preoperatively. It reduces the vascularity of the gland