The adrenal cortex

- The adrenal glands are divided into two embryologically and functionally distinct parts.
- The adrenal cortex is part of the hypothalamic–pituitary– adrenal endocrine system.
- Morphologically, the adult adrenal cortex consists of three layers.
- The outer thin layer (zona glomerulosa) secretes only aldosterone
- . The inner two layers (zona fasciculata and zona reticularis) form a functional unit and secrete most of the adrenocortical hormones.
- In the fetus there is awider fourth layer, which disappears soon after birth.
- One of its most important functions during fetal life is, together with the adrenal cortex, to synthesize oestriol, in association with the placenta.
- The adrenal medulla is part of the sympathetic nervous system.

CHEMISTRY AND BIOSYNTHESIS OF STEROIDS

- Steroid hormones are derived from the lipid cholesterol.)27 carbon atoms and the lettering of the four rings).
- The products of cholesterol are also indicated.
- If the molecule contains 21 carbon atoms, it is referred to as a C21 steroid.
- The carbon atom at position 21 of the molecule is written as C-21.
- The side chain on C-17 is the main determinant of the type of hormonal activity

- The first hormonal product of cholesterol is pregnenolone.
- The final product is dependent upon the tissue and its enzymes. The zona glomerulosa secretes aldosterone, produced by 18-hydroxylation.
- Synthesis of this steroid is controlled by the renin–angiotensin system and not normally by ACTH.
- Although ACTH is important for maintaining growth of the zona glomerulosa, deficiency does not significantly reduce output.
- The zonae fasciculata and reticularis synthesize and secrete two groups of steroid:

Cortisol, a glucocorticoid (the most importantC21 steroid), is formed by progressive addition of hydroxyl groups at C-17, C-21 and C-11.

Androgens (for example androstenedione) are formed after the removal of the side chain to produce C19 steroids.

ACTH secreted by the anterior pituitary gland stimulates synthesis of these two steroid groups.

Its secretion is influenced by negative feedback from changes in plasma cortisol concentrations

. Impaired cortisol synthesis due to an inherited 21α-hydroxylase or 11-b-hydroxylase deficiency (congenital adrenal hyperplasia) results in increased ACTH stimulation with increased activity of both pathways.

The resultant excessive androgen production may cause hirsutism or virilization.

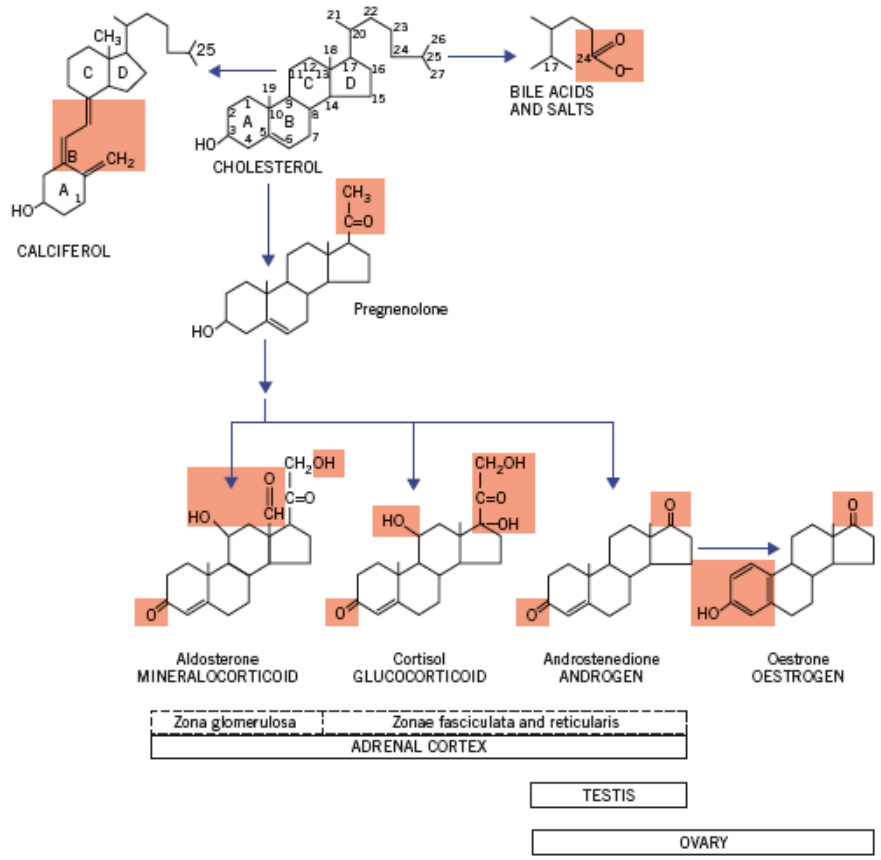


Figure 8.1 Numbering of the steroid carbon atoms of cholesterol and the synthetic pathway of steroid hormones; the chemical groups highlighted determine the biological activity of the steroid.

PHYSIOLOGY

The adrenocortical hormones can be classified int groups depending on their predominant physiological effects.

Glucocorticoids

Cortisol and corticosterone are naturally occurring glucocorticoids.

They stimulate gluconeogenesis and the breakdown of protein and fat, that is, they antagonize some of insulin's action.

Glucocorticoids in excess may impair glucose tolerance and alter the distribution of adipose tissue.

Cortisol helps maintain the extracellular fluid volume and normal blood pressure.

Circulating cortisol is bound to cortisol-binding globulin (CBG; transcortin) and to albumin.

At normal concentrations, only about 5 % of the total unbound & physiologically active.

Plasma CB is almost fully saturated, so that increased cortisol secretion causes a disproportionate rise in the free active fraction.

Cortisone is not secreted in signifycant amounts by the adrenal cortex.

It is biologically inactive until it has been converted in vivo to cortisol (hydrocortisone).

Glucocorticoids are conjugated with glucuronat and sulphate in the liver to form inactive metabolites which, are more water soluble than the mainly protein-bound parent hormones, can b excreted in the urine.

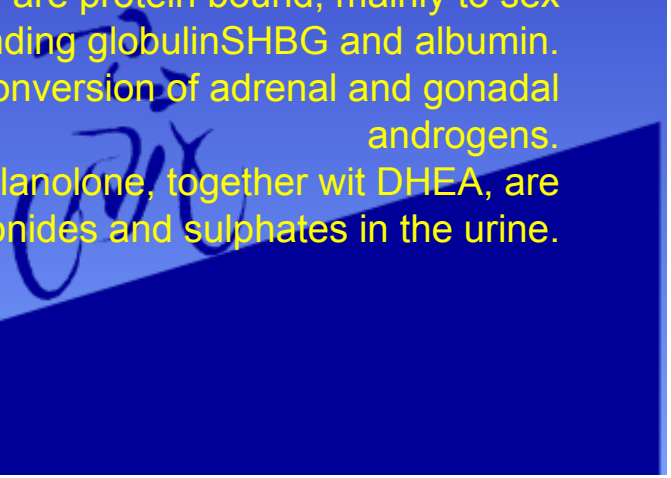
- **Mineralocorticoids**
- In contrast to other steroids, aldosterone is no transported in plasma bound to specific proteins.
- It stimulates the exchange of sodium for potassium and hydrogen ions across cell membranes and its renal action is especially important for sodium and water homeostasis.
- Like the glucocorticoids, it is inactivated by hepatic conjugation and is excreted in the urine

.

- There is overlap in the actions of C21 steroids. Cortisol, in particular, may have a signifycant mineralocorticoid effect at high plasma concentrations when the free fraction is significantly increased.

- # Adrenal androgens

The main adrenal androgens are dehydroepiandrosteron (DHEA), its sulphate (DHEAS) an androstenedione.
They promote protein synthesis and are only weakly androgenic at physiological concentrations.
Testosterone, the most powerful androgen, is synthesized in the testes or ovaries bu not in the adrenal cortex.
Most circulating androgens like cortisol, are protein bound, mainly to sex hormone binding globulinSHBG and albumin.
There is extensive peripheral interconversion of adrenal and gonadal androgens.
The end products androsterone and aetiocholanolone, together wit DHEA, are conjugated in the liver and excreted a glucuronides and sulphates in the urine.



THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

- The hypothalamus, anterior pituitary gland and adrenal cortex form a functional unit – the hypothalamic–pituitary–adrenal axis.
- Cortisol is synthesized and secreted in response to ACTH from the anterior pituitary gland.
- The secretion of ACTH is dependent on corticotrophinreleasing hormone (CRH), released from the hypothalamus.
- High plasma free cortisol concentrations suppress CRH secretion (negative feedback) and alter the ACTH response to CRH, thus acting on both the hypothalamus and the anterior pituitary gland (Fig.).

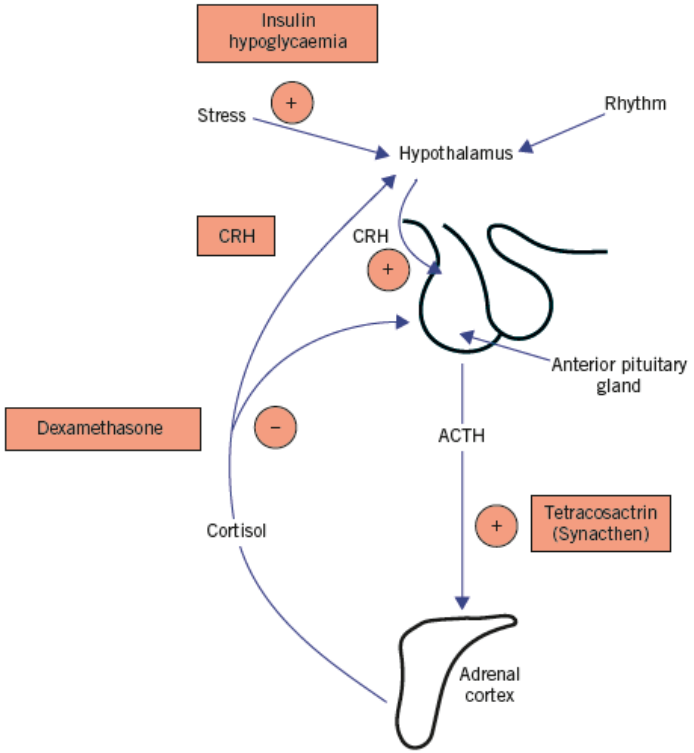
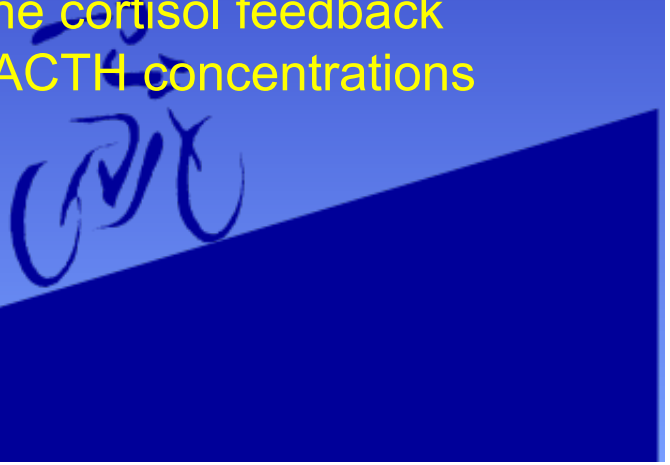


Figure 8.2 The factors controlling the secretion of cortisol from the adrenal gland, including the site of action of dynamic function tests (shaded). +, stimulates; –, inhibits; ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone.

- The melanocyte-stimulating effect of high plasma concentrations of ACTH, or related peptides, causes skin pigmentation in two conditions associated with low plasma cortisol concentrations:
- Addison's disease,
- Nelson's syndrome: after bilateral adrenalectomy for Cushing's disease, removal of the cortisol feedback causes a further rise in plasma ACTH concentrations from already high levels.

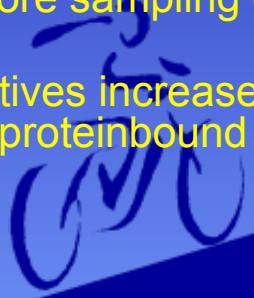


Inherent rhythms and stress

- ACTH is secreted episodically, each pulse being followed 5-10 min later by cortisol secretion.
- These episodes are most frequent in the early morning (between the fifth and eighth hour of sleep) and least frequent in the few hours before sleep.
- Plasma cortisol concentrations are usually highest between about 7:00 and 09:00 h and lowest between 23:00 and 04:00h.
- Inappropriately high plasma cortisol concentrations at any time of day suppress ACTH secretion. This effect can be tested by the dexamethasone suppression test.
- Loss of circadian rhythm is one of the earliest features of Cushing's syndrome.
- Stress, either physical or mental, cause sustained ACTH secretion
- An inadequate stress response may cause acute adrenal insuffi ciency.
- Stress caused by insulin-induce hypoglycaemia can be used to test the axis.

Factors affecting plasma cortisol concentration

- Plasma cortisol is usually measured by immunoassay, but the antibody may cross-react with other steroids or drugs
- . Factors that may affect results include hydrocortisone)cortisol), cortisone (converted to cortisol by metabolism) and prednisolone, which may contribute to the ‘cortisol’ concentration of some immunoassay methods.
- Thus, it is recommended either that the patient is prescribed dexamethasone (which is less likely to cross-react with cortisol assays) or, if possible, that the prednisolone is gradually reduced and then stopped for about 3 days before sampling depending upon clinical context
- . Oestrogens and some oral contraceptives increase the plasma CBG concentration, and therefore the proteinbound cortisol concentration.



DISORDERS OF THE ADRENAL CORTEX

- The main disorders of adrenocortical function are shown in Table

Table 8.1 Disorders of adrenocortical function

Altered hormone secretion	Associated clinical disorder
Hypersecretion	
Cortisol	Cushing's syndrome
Aldosterone	Primary hyperaldosteronism (Conn's syndrome)
Androgens	Congenital adrenal hyperplasia Adrenocortical carcinoma
Hyposecretion	
Cortisol and aldosterone	Primary adrenal disorders, e.g. Addison's disease or congenital adrenal hyperplasia
Cortisol and adrenocorticotrophic hormone	Adrenal insufficiency secondary to pituitary disease

Adrenocortical hyperfunction

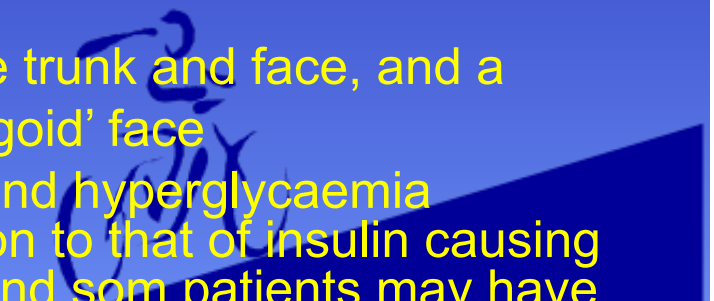
- **Cushing's syndrome**

Cushing's syndrome is mainly caused by an excess of circulating cortisol but also other steroids such as androgens.

Many of the clinical and metabolic disturbances can be explained by glucocorticoid excess

. The clinical and metabolic features may include the following:

- Obesity, typically involving the trunk and face, and a characteristic round, red 'cushingoid' face
- Impaired glucose tolerance and hyperglycaemia Cortisol has the opposite action to that of insulin causing increased gluconeogenesis, and som patients may have diabetes mellitus



- Increased protein catabolism, which also increases urinary protein loss. associated with proximal muscle wasting with weakness, thinning of the skin and osteoporosis. The tendency to bruising and the purple striae (most obvious on the abdominal wall) are probably due to this thinning.
- Hypertension, caused by urinary retention of sodium and therefore of water, which are due to the mineralocorticoid effect of cortisol. Increased urinary potassium loss may cause hypokalaemia.
- Androgen excess, which may account for the common findings of greasy skin with acne vulgaris and hirsutism, and menstrual disturbances in women.
- Psychiatric disturbances, such as depression.

Laboratory fi ndings include a hypokalaemic alkalosis, leucocytosis and eosinophilia.

- ***Causes of Cushing's syndrome***

One of the most common causes of Cushing's syndrome is iatrogenic and related to excessive steroid treatment. Increased endogenous cortisol production may be due to hyperstimulation of the adrenal gland by ACTH, either from the pituitary gland or from an 'ectopic' source,or due to largely autonomous secretion by an adrenal tumour such as an adenoma or carcinoma.

The secretion of ACTH is increased in the following conditions.