

# ADRENAL CORTEX

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# Adrenal Gland

- 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 (zonae fasciculata and reticularis synthesise) form a functional unit and secrete most of the adrenocortical hormones. In the fetus there is a wider fourth layer, which disappears soon after birth.
- One of its most important functions during fetal life is, together with the adrenal cortex, to synthesise 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. Figure below shows the internationally agreed numbering of the 27 carbon atoms of steroid molecules 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 C<sub>21</sub> 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, but substitutions in other positions modify activity within a particular group.

The first hormonal product of cholesterol is **pregnenolone** several molecules diverge from it.

The final product is dependent upon the tissue and its enzymes.

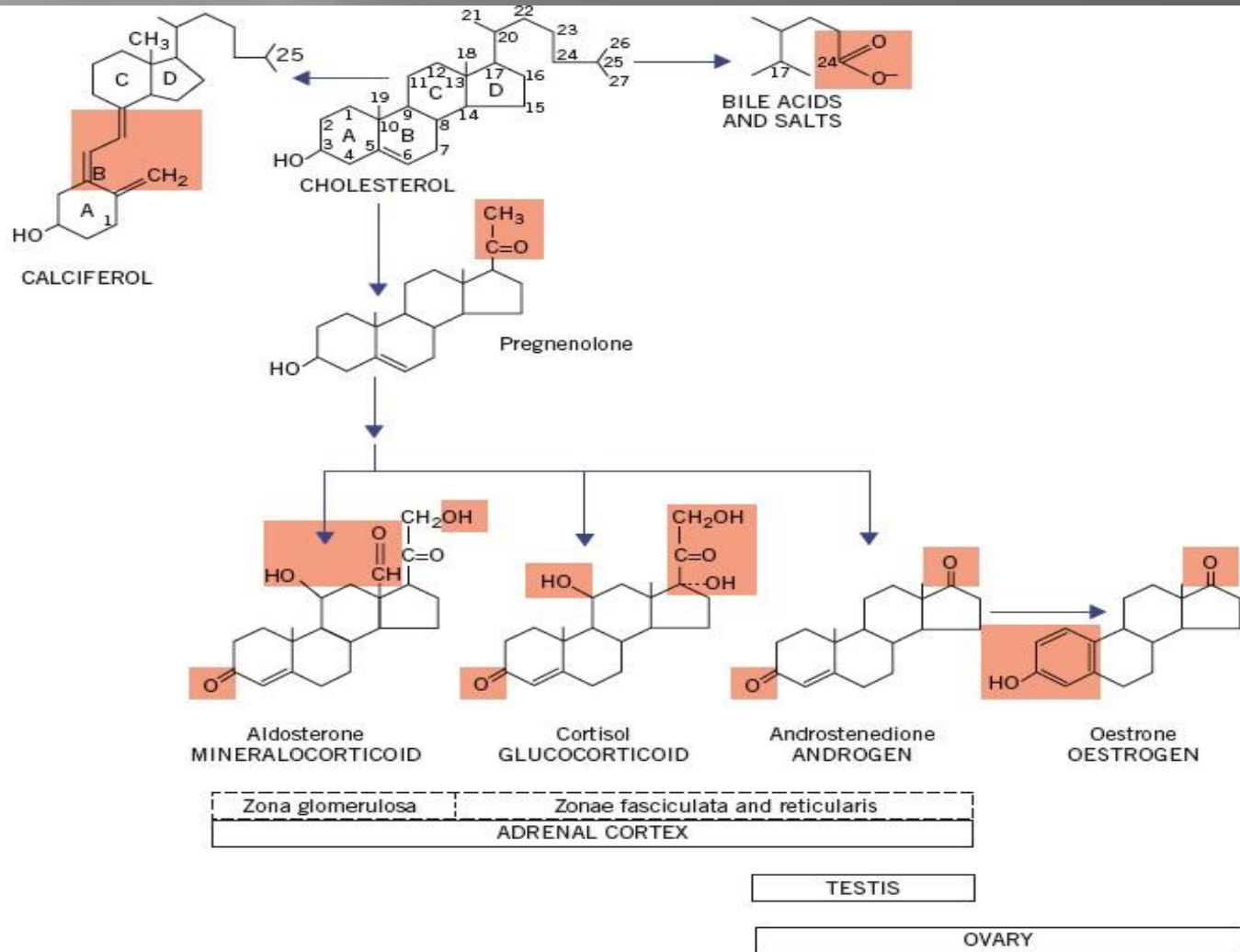
. Synthesis of this steroid is controlled by the and not normally by adrenocorticotrophic hormone (ACTH)

. 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 important C21 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

Adrenocorticotrophic hormone 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, for example, to an inherited 21- $\alpha$ -hydroxylase or 11- $\beta$ -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 into 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 per cent of the total is unbound and physiologically active.



- It is biologically inactive until it has been converted in vivo to cortisol (hydrocortisone )
- Glucocorticoids are conjugated with glucuronate and sulphate in the liver to form inactive metabolites, which, because they are more water soluble than the mainly protein-bound parent hormones, can be excreted in the urine
- In contrast to other steroids, aldosterone is not 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

# Adrenal androgens

- The main adrenal androgens are dehydroepiandrosterone (DHEA), its sulphate (DHEAS) and 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 but not in the adrenal cortex. Most circulating androgens, like cortisol, are protein bound, mainly to sexhormone-binding globulin and albumin.
- There is extensive peripheral interconversion of adrenal and gonadal androgens. The end products, androsterone and aetiocholanolone, together with DHEA, are conjugated in the liver and excreted as glucuronides and sulphates in the urine.

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 corticotrophin-releasing 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.



# DISORDERS OF THE ADRENAL CORTEX

## 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 some patients may have diabetes mellitus.

Increased protein catabolism, which also increases urinary protein loss. Thus, there is a negative nitrogen balance 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 findings 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.
- **Cushing's disease** It is associated with bilateral adrenal hyperplasia, often secondary to a basophil adenoma of the anterior pituitary gland
- **Ectopic ACTH secretion** In this condition, usually from a small-cell carcinoma of the bronchus, ACTH concentrations may be high enough to cause skin pigmentation. The patient may have weight loss with cachexia. One metabolic complication is a hypokalaemic alkalosis. The clinical features may be indistinguishable from those of Cushing's disease, although sometimes patients do not have the characteristic cushingoid features as the cortisol rises so quickly

## PRIMARY ADRENOCORTICAL HYPOFUNCTION ADDISON'S DISEASE

. Addison's disease is caused by bilateral destruction of all zones of the adrenal cortex, usually as the result of an autoimmune process. The association of Addison's disease with hypoparathyroidism and mucocutaneous candidiasis is described as polyglandular autoimmune syndrome type 1 and has autosomal recessive inheritance.

. Polyglandular autoimmune syndrome type 2 occurs when Addison's disease is associated with type 1 diabetes mellitus and autoimmune thyroid disease, either Hashimoto's thyroiditis or Graves' disease, and is also related to human leucocyte antigen (HLA)-B8 and DR-3 types.

Secondary adrenal hypofunction (adrenocorticotrophic hormone deficiency) Adrenocorticotrophic hormone release may be impaired by disorders of the hypothalamus or the anterior pituitary gland, most commonly due to a tumour or infarction

- Corticosteroids suppress ACTH release and, if such drugs have been taken for a long time, the ACTH-releasing mechanism may be slow to recover after the steroid is stopped. There may be temporary adrenal atrophy after prolonged lack of stimulation. Extensive destruction of the anterior pituitary gland may cause panhypopituitarism .but, if it is only partial, ACTH secretion may be adequate for basal requirements.

Adrenocortical deficiency may then only become clinically evident under conditions of stress, which may precipitate acute adrenal insufficiency. The most common causes of stress are infection and surgery.

Patients may present with non-specific symptoms such as weight loss and tiredness. Hypoglycaemia may occur because of marked insulin sensitivity. Unlike primary adrenal hypofunction, pigmentation is absent because plasma ACTH concentrations are not raised



## CONGENITAL ADRENAL HYPERPLASIA

The term congenital adrenal hyperplasia (CAH) embraces various defects involving enzymes of cortisol or aldosterone synthesis. Many of the enzymes involved in cortisol and aldosterone pathways are cytochrome p450 proteins designated CYP. CYP21 refers to 21-hydroxylase, CYP11B1 refers to 11- $\beta$ -hydroxylase and CYP17 to 17- $\alpha$ -hydroxylase.

All forms of CAH are rare. An inherited deficiency (usually autosomal recessive) of one of the enzymes involved in the biosynthesis of cortisol, with a low plasma concentration, causes a high rate of secretion of ACTH from the anterior pituitary gland.

This results in hyperplasia of the adrenal cortex, with increased synthesis of cortisol precursors before the enzyme block. The precursors may then be metabolized by alternative pathways, such as those of androgen synthesis.

- Increased androgen production may cause:
  - female pseudohermaphroditism*, by affecting the development of the female genitalia in utero; ambiguous genitalia may show phallic enlargement, clitoromegaly and early pubic hair,
  - virilization in childhood*, with phallic enlargement in either sex, development of pubic hair and a rapid growth rate, *milder virilization in females* at or after puberty, with amenorrhoea.

# PRIMARY HYPERALDOSTERONISM (CONN'S SYNDROME)

Primary hyperaldosteronism (PH) is considered an important cause of secondary hypertension in perhaps as many as 5–15 per cent of cases, particularly in the face of hypokalaemia and kaliuria (e.g. urinary potassium more than 20 mmol/L)