The adrenal glands and their functions

Abstract

The adrenal glands secrete hormones essential for metabolism, regulation of blood pressure, and sodium and glucose homeostasis. Hypo- or hypersecretion of these hormones is life threatening. Understanding the physiological functions of adrenal hormones is a prerequisite to the management of adrenal gland disease.

Adrenal structure and embryology

The adrenal glands are retroperitoneal structures lying supero-medial to both kidneys. They have a functionally distinct outer cortex and inner medulla. The adrenal cortex is composed of a subcapsular zona glomerulosa (15% of cortex), which secretes aldosterone. The zona fasciculata beneath it (75% of cortex) is the main site for glucocorticoid and androgen synthesis. The inner zona reticularis secretes adrenal androgens and glucocorticoids. The medulla is a modified sympathetic ganglion and secretes catecholamines (adrenaline, noradrenaline, dopamine).

In fetal life, the adrenal cortex (derived from the mesoderm) consists of a larger 'fetal' and 'definitive' zone, the latter developing into the adult adrenal cortex and the former disappearing after birth. The fetal zone produces cortisol, corticosterone, dehydroepiandrosterone (DHEA) and DHEA sulphate. The latter two hormones are transported to the placenta for oestrogen synthesis (feto-placental unit). Fetal exposure to high levels of maternal corticosteroids has been suggested as a contributor to low birth weight, and metabolic and endocrine problems in post-natal life.

The adrenal medulla is derived from neural crest cells, which also form paraganglia around the aorta. In fetal life, paraganglia cells (organ of Zuckerkandl) are the main source of catecholamines.

Steroid hormone biosynthesis

The adrenal cortex secretes the steroid hormones, glucocorticoids (cortisol, corticosterone), mineralocorticoid (aldosterone) and androgens (DHEA, DHEA sulphate, androstenedione). An outline of the biosynthesis of these hormones is given in panel 1 and figure 1. Adrenal androgens undergo peripheral conversion to testosterone, dihydrotestosterone and oestrogens.

Enzyme expression in adrenal zones (figure 1)

The enzyme P450c17 (17 α -hydroxylase) is absent in the zona glomerulosa, and cortisol and androgen synthesis does not take place here. The glomerulosa contains P450c11AS (aldosterone synthase or CYP11B2), which converts 11-deoxycorticosterone to aldosterone. The zona fasciculata has greater expression of 3 β -hydroxysteroid dehydrogenase and produces mainly cortisol and corticosterone. The reticularis has co-factors for the 17, 20-lyase activity of P450c17 needed to produce androgens, and the enzyme required for DHEA sulphate formation.

Transport and metabolism

Its high protein binding (to transcortin and albumin) confers a long half-life to cortisol. Unbound cortisol is physiologically active whereas the bound form acts as a

Panel 1. Steps in steroid hormone synthesis.

1. Transport of cholesterol from the cytoplasm to the inner mitochondrial membrane [occurs in all parts of the cortex] by steroidogenic acute regulatory protein (StAR).
2. Removal of six carbon side chain from cholesterol forms pregnenolone. This involves cytochrome P450sc (also termed CYP11A or cholesterol desmolase).
3. Transport of pregnenolone to the smooth endoplasmic reticulum (SER).
4. The enzyme P450c17 (17 α hydroxylase) converts pregnenolone to 17 α -hydroxypregnenolone (also converts progesterone to 17 α -hydroxyprogesterone)
5. 3 β -hydroxysteroid dehydrogenase converts 17 α -hydroxypregnenolone to 17 α -progesterone (also converts pregnenolone to progesterone).
6. P450c21 (also called 21 β -hydroxylase) converts the 17 α -hydroxypregnenolone to 11-deoxycortisol (and converts progesterone to 11-deoxycorticosterone).
7. The deoxycortisol and deoxycorticosterone are transported to the mitochondria where (in the fasciculata and reticularis), the final conversion to cortisol and corticosterone respectively takes place. This is by the enzyme P450c11 (also called 11 β -hydroxylase).
8. In the glomerulosa, the enzyme P450c11AS causes deoxycorticosterone to form aldosterone.
9. In the fasciculata and reticularis, P450c17 (17,20 lyase) converts 17 α -hydroxypregnenolone to DHEA (also converts 17 α -hydroxyprogesterone to androstenedione).

Figure 1. Outline of pathways for biosynthesis of adrenal hormones. Enzymes are indicated in italics.

hormone reservoir. Elevated transcortin levels (as in high oestrogen states) raise the total but not the free cortisol level. Aldosterone has a shorter half-life compared to cortisol. Glucocorticoids and mineralocorticoids undergo hepatic conversion to less active compounds and conjugation before renal excretion. A small proportion is excreted unchanged in the urine (this increases in cortisol hypersecretion).

Mechanism of steroid hormone action

Cortisol crosses the cell membrane to act on cytoplasmic receptors containing a heat shock protein. Following cortisol binding, the heat shock protein dissociates and the activated hormone receptor complex binds DNA to regulate the expression of genes. Steroid hormones use as yet unexplained mechanisms also for their actions.

Glucocorticoid functions

1. Intermediary metabolism. Raises blood glucose (mainly during fasting) by increasing hepatic gluconeogenesis and reducing peripheral utilisation of glucose; increasing hepatic glycogen synthesis, lipolysis and muscle breakdown.

2. Permissive effect. Enables other hormones to exert effects (eg. glucagon, catecholamines).
3. Vascular effects. Needed for catecholamine induced vasoconstriction.
4. Water balance using unknown mechanisms.
5. Essential for normal functioning of the central nervous, cardiovascular, renal, endocrine systems.
6. Blood, lymphatic and immune systems. Decreases eosinophil, basophil and lymphocyte counts, and increases neutrophil and erythrocyte counts. Reduces leucocyte and chemical mediator response to injury and infection. Reduces the size of lymph nodes and thymus.
7. Anti-stress effect. When homeostasis is threatened (eg. surgery, trauma) secretion is increased.
8. Connective tissue and calcium. Inhibits fibroblast proliferation, collagen synthesis, new bone formation and increases calcium loss through gut and kidney.
9. Fetal effects. Essential for maturation of the central nervous system, lungs (surfactant production).

Aldosterone and its functions

Aldosterone binds cytoplasmic mineralocorticoid receptors in P (principal) cells of the renal collecting ducts,

parts of the colon, and sweat and salivary glands. It causes epithelial sodium channels (ENaCs) to move from the cytoplasm to the epithelial membrane and increases production and activity of these channels. ENaCs enable reabsorption of Na^+ in exchange for K^+ and H^+ ions. The resulting sodium and water retention is essential for maintenance of the extracellular fluid volume.

Mineralocorticoid activity of glucocorticoids

The adrenal glucocorticoids have high affinity to the aldosterone receptor. In aldosterone responsive cells, 11β -hydroxysteroid dehydrogenase converts cortisol and corticosterone to a less active metabolites but does not metabolise aldosterone. In cortisol hypersecretion, this enzyme's capacity is exceeded and cortisol exerts aldosterone-like effects. Ingestion of large amounts of liquorice (contains glycyrrhetic acid) can inactivate this enzyme, causing mineralocorticoid effects.

Regulation of zona fasciculata and reticularis

The hypothalamo-pituitary-adrenal axis is outlined in figure 2. The paraventricular nuclei of the hypothalamus secrete corticotropin releasing hormone (CRH). It is transported via the hypothalamo-pituitary portal circulation and stimulates the anterior and intermediate lobes of the pituitary gland to secrete adrenocorticotrophic hormone (ACTH).

ACTH stimulates the synthesis and release of glucocorticoids. It also increases the formation of P450 enzymes and increases the sensitivity of the adrenal cortex to ACTH stimulation. In ACTH deficiency, there is a reduction in the size and responsiveness of the adrenal cortex. ACTH binds melanotropin receptors and increases skin pigmentation. A rise in the free (unbound) cortisol inhibits ACTH and CRH secretion (negative feedback regulation).

Regulation of zona glomerulosa (figure 3)

The secretion of aldosterone is regulated mainly by angiotensin II (AT II) and K^+ . ACTH has a transient effect in increasing aldosterone secretion. Aldosterone secretion is regulated by the extracellular fluid volume (and pressure) detected by the renin secreting, juxtaglomerular apparatus of renal glomerular afferent arterioles. AT II increases the conversion of cholesterol to pregnenolone and corticosterone to aldosterone. Elevated levels of K^+ (and significantly low Na^+) exert a similar mechanism of action.

Circadian rhythms of secretion

ACTH has a rhythmical, daily (circadian) secretion. Bursts of secretion, stimulated by hypothalamic CRH occur between 0400 and 1000 hours. The frequency of secretion is reduced in the evening. Stress, pain or psychological factors (anxiety, depression), increase ACTH secretion via hypothalamic centres.

Figure 2. Regulation of cortisol secretion.

Figure 3. Regulation of aldosterone secretion

Congenital adrenal hyperplasia

Deficiencies of enzymes involved in steroid hormone synthesis result in depletion of hormones synthesised by the deficient enzyme and an increase in the level of the precursor hormones and ACTH. Variable symptoms related to deficiency or excess of glucocorticoids, mineralocorticoids, adrenal androgens or combinations of these occur. The five recognised enzyme deficiencies and their clinical patterns are summarised in table 1.

The adrenal medulla

The adrenal medulla secretes adrenaline, noradrenaline and dopamine, all derived from tyrosine

(figure 4). Some enzymes in catecholamine synthesis are induced by glucocorticoids (cortisol deficiency reduces catecholamine secretion). Catecholamines are stored in granules, complexed with ATP and a protein (chromogranin). Secretion is stimulated by acetylcholine released at preganglionic neurones innervating the medulla. Catecholamines have a half-life of a few minutes. They are metabolised to metanephrine, normetanephrine and vanillylmandelic acid, and excreted by the kidneys. Following adrenalectomy, there is an initial fall and later rise of catecholamines, but their source is unknown.

Adrenaline and noradrenaline act on α (type 1 and 2) and β (type 1, 2 and 3) adrenoceptors. They mediate the

Figure 4. Catecholamine synthesis

Table 1. Enzyme deficiencies and hormone anomalies in the adrenogenital syndrome

Enzyme deficiency	Substrate	Synthesised hormones	Glucocorticoid	Mineralocorticoid	Androgens
Steroidogenic acute regulatory protein (STAR)		Mediates cholesterol transport across mitochondrial membrane	Deficiency	Deficiency (salt losing)	Deficiency (ambiguous genitalia in males)
3 β -hydroxysteroid dehydrogenase (3 β -HSD)	Pregnenolone, 17-OH Pregnenolone, DHEA	Progesterone, 17-OHP, Androstenedione	Deficiency	Deficiency (salt losing)	Slight increase (occasional virilisation of females; ambiguous genitalia in males)
17 α -hydroxylase	Pregnenolone Progesterone	17 α OH Pregnenolone 17 α OH Progesterone	Mild Deficiency	Excess (hypertension, hypokalaemia)	Deficiency (ambiguous genitalia in males, amenorrhoea in females)
21-hydroxylase (95% of cases)	Progesterone 17OH Progesterone	11 deoxycorticosterone 11-deoxycortisol	Deficiency	Deficiency (75%)	Excessive (virilisation of females)
11 β -hydroxylase (>4% of cases)	11 deoxycorticosterone 11-deoxycortisol	Corticosterone Cortisol	Deficiency	Excess (hypertension, hypokalaemia)	Excessive (virilisation of females)

"flight or fight response" by increasing the rate and force of cardiac contraction, α_1 mediated generalised vasoconstriction, and β_2 mediated vasodilation in the heart and skeletal muscles. They also increase alertness. Their metabolic effects include increasing plasma glucose and metabolic rate.

The principles of testing the adrenal axis

Investigating the functions of the adrenal axis is complex. The following is an outline that will be expanded in the later sections.

- Plasma or serum hormone levels measured using radioimmuno assays or high-pressure liquid (or gas) chromatography (HPLC) is highly accurate. Check if the results are for free or total hormone levels and the reference range for the laboratory.
- Timing of samples should be based on circadian rhythms of secretion. Low levels of cortisol in the early morning (when these levels should be at their peak) are suggestive of hypo-secretion, and high levels at midnight are suggestive of hyper-secretion.
- ACTH in combination with cortisol helps to differentiate between adrenal versus pituitary/hypothalamic disease: low morning cortisol associated with high ACTH suggests adrenal disease but if the ACTH is also low, pituitary (or hypothalamic) dysfunction is suggested. In cortisol excess, a low ACTH level is suggestive of non-ACTH dependent secretion of cortisol.
- Stimulation tests (eg. the Synacthen test) are used for the diagnosis of adrenal gland hypofunction. Results have to be compared with expected levels and further tests (eg. metyrapone test) may be required to differentiate between pituitary or hypothalamic hypofunction.
- Suppression tests attempt to use the principle of feedback inhibition to assess the presence of an inappropriately elevated hormone level which is not suppressible through negative feedback regulation (eg. the dexamethasone suppression test in cortisol excess).
- Urinary assays are useful to assess hormones with a short half-life (eg. catecholamine metabolites) or to detect excessive urinary excretion (eg. in cortisol excess urinary free cortisol rises). Metabolites of cortisol (17-hydroxycorticosteroids, 17 ketogenic steroids) and androgens (17-ketosteroids) are less reliable but help in confirming diagnosis or for monitoring treatment.

Further reading

General

1. Johnson L. Adrenal glands. In: Essential Medical Physiology 2nd edition Philadelphia/ New York: Lippincott-Raven; 1998.

CME articles (Series 2)

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2. Ganong W. The adrenal medulla and adrenal cortex. In: Review of medical physiology 22nd edition. Boston: McGraw Hill; 2005.
3. Granner D. Hormone action and signal transduction. In: Murray R, Granner D, Rodwell V eds. Harper's illustrated Biochemistry 27th Edition. New York: McGraw Hill Lange; 2006.

Endocrine testing

1. Nieman LK. Dynamic evaluation of adrenal hypofunction.

Journal of Endocrinological Investigation 2003; **26** (Suppl): 74-82 [Abstract].

2. Dickstein G. The assessment of the hypothalamo-pituitary-adrenal axis in pituitary disease: are there short cuts? *Journal of Endocrinological Investigation* 2003; **26** (Suppl): 25-30 [Abstract].

Adrenogenital syndrome

1. Speiser P, and White P. Congenital adrenal hyperplasia. *New England Journal of Medicine* 2003; **349**: 776-88.

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