Endocrinology – adrenal

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The adrenals sit atop the kidneys (hence the name) and are surrounded by perirenal fat.
Consider the cortex and medulla separately.

Adrenal cortex

The adult cortex has three subdivisions. From the outside in:

G	**zona glomerulosa**	makes **mineralocorticoids** (esp. aldosterone)
F	**zona fasciculata**	makes **glucocorticoids** (esp. cortisol)
R	**zona reticularis**	makes **sex steroids** (esp. dehydroepiandrosterone, testosterone, progesterone)

Glucocorticoids – nature

- Glucocorticoids are 21-carbon steroids.
- **Steroid biosynthesis.** You should know that cholesterol (27-carbon, "C27") is converted to progesterone (C21), which can be converted to adrenocorticosteroids (C21) or androgens (C19). Androgens can be aromatised (by *aromatase*) to oestrogens. You don't need to know the full picture, which is extremely complex.
- There is very little storage of steroids; they're made on demand.
- Corticosteroids bind to **cortisol-binding globulin** (CBG) in plasma (~90% is bound). This contributes to the long half-life, ~80 minutes. They are destroyed in the liver. CBG is also made in the liver. It is the free, unbound cortisol that is available to target tissues.
- Both glucocorticoids and mineralocorticoids are fat-soluble and cross cell membranes. They bind to specific nuclear receptors, which bind to DNA and initiate gene transcription.

Glucocorticoids – functions

- **Intermediary metabolism.** Glucocorticoids affect carbohydrate, lipid and protein metabolism. They have anabolic actions on the liver, promoting gluconeogenesis. They have catabolic actions on skeletal muscle and adipocytes, inhibiting glucose uptake and causing proteolysis/lipolysis, which frees FFAs and amino acids for gluconeogenesis in the liver. Glucocorticoids therefore elevate blood glucose and antagonise insulin.
- **Permissive actions.** Glucocorticoids are required for the sympathetic/adrenal system to function: under conditions of stress, in the absence of glucocorticoids, there is vascular collapse leading to ☠**death.** GCs are necessary for catecholamine synthesis (in nerve terminals and in the adrenal). They allow lipolytic enzymes to be activated by catecholamines. Without GCs, their permissive effect on liver gluconeogenesis and fat metabolism is lost and body temperature falls. [Many other permissive effects, including a major role in fetal development.]
- **Role in reproduction.** Possible role in parturition (certainly true in sheep). Permits lactogenesis.
- **Nervous system effects.** Required for hippocampal neuron survival (though can also be toxic in high doses).
- **Anti-inflammatory and immunosuppressive effects.** Above physiological concentrations, glucocorticoids inhibit inflammatory and allergic reactions; they are frequently used for this in medicine. Side effect: vulnerability to infection. N.B. High doses also cause catabolism of skeletal muscle and bone (→osteoporosis).
- Glucocorticoid release is part of the **stress response.**

Glucocorticoids – control

- Glucocorticoid release is regulated solely by **ACTH** (adrenocorticotrophic hormone, from the anterior pituitary). ACTH is also *trophic* for the zona fasciculata (i.e. withdraw ACTH and the z.f. shrinks).
- ACTH is a peptide hormone that acts via a G-protein and ↑cAMP. Its release is influenced by stress, and shows a nycthemeral rhythm (highest just after waking). Its release is stimulated by **CRH** (corticotropin-releasing hormone) from the hypothalamus.
- **Negative feedback:** cortisol suppresses both ACTH and CRH secretion.
- Clinical relevance: if you give exogenous cortisol, ACTH will be suppressed, and the z.f. will regress. If you suddenly withdraw the exogenous steroid, the z.f. will be unable to cope with the demand and you will have precipitated adrenocortical insufficiency.

Mineralocorticoids – nature and function

- Aldosterone acts primarily at the **distal convoluted tubules** of the kidney to **increase Na^+ reabsorption.** This sodium uptake is balanced by passive **K^+ loss,** or by H^+ loss if potassium levels are low.
- Some think its main role is the control of K^+.
- It also promotes sodium reabsorption/potassium excretion into sweat, saliva and GI secretions.
- Aldosterone is a C21 steroid and works by inducing protein synthesis, like glucocorticoids.
- The 'mineralocorticoid' receptor has equal affinity for aldosterone and for the glucocorticoids cortisol and corticosterone, which circulate at much higher levels. So how does the system respond selectively to the aldosterone level? There is a **cortisol→cortisone shunt** in mineralocorticoid target tissues, which effectively destroys glucocorticoids in the cell and means that aldosterone is the only steroid that can act (see also liquorice, below). The enzyme responsible is 11β-hydroxysteroid dehydrogenase.

Mineralocorticoids – control

- Secretion is controlled by the **renin–angiotensin system.**
- The z.g. does *not* depend on the pituitary for support.
- **Decreased renal blood flow** (suggesting hypovolaemia[1]) and **sympathetic activity** promote renin secretion by the juxtaglomerular apparatus (JGA).
- ↑Renin → increased conversion of angiotensin-I to **angiotensin-II** by angiotensin-converting enzyme (ACE) → acts on z.g. cells via G-proteins (PLC, IP_3 pathway).
- **High K^+** is a direct stimulus for aldosterone secretion, as are **ACTH** and **low Na^+** (weak direct effect).
- Atrial natriuretic peptide (ANP) signals a "full" vascular system and inhibits aldosterone synthesis.

Sex steroids

The zona reticularis depends on pituitary support. We will cover sex steroids in the reproduction course.

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[1] Remember the "catch-22": in heart failure, the kidneys are underperfused because of cardiac inadequacy, not because there is hypovolaemia; nevertheless, renin is secreted, more sodium (and therefore water) is retained and the load on the heart increases. A vicious cycle from which ACE inhibitors have rescued many.

Adrenal medulla

The medulla makes catecholamines, especially **adrenaline.** It is not essential for life.
Catecholamine biosynthesis, which you should know:

tyrosine	
↓	*tyrosine hydroxylase (cytoplasm)*
DOPA	
↓	*DOPA decarboxylase (cytoplasm)*
dopamine (DA)	
↓	*dopamine β-hydroxylase (secretory granule)*
noradrenaline (NA)	
↓	*PNMT [phenylethanolamine N-methyltransferase] (cytoplasm)*
adrenaline	

- Blood from the adrenal cortex drains into the medulla. Obviously, this blood is rich in steroids; this steroid activity is needed for the enzyme PNMT to work, so the medulla depends to some extent upon a functioning cortex.
- Embryologically, the medulla is derived from *neural crest*.
- Adrenaline is the predominant hormone that the medulla secretes into the blood. Noradrenaline is primarily a neurotransmitter, but it also leaks into the blood from sympathetic nerve terminals (e.g. on vascular smooth muscle).
- Catecholamines are stored in secretory vesicles from which they are released by exocytosis. The medulla is under **sympathetic nervous control.**
- Plasma half-life is ~20 seconds. Breakdown is by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO)[2].
- Receptors are α_1, α_2, β_1, β_2 adrenoceptors with which you should be familiar. Their levels are modulated by gonadal and adrenal steroid hormones (permissive effects), and the effect of the sympathoadrenal system is enhanced by thyroid hormones.

Adrenaline – function

Consider the "sympathoadrenal" system as a functional unit. NA is released by neurons for local autonomic control; adrenaline is a global message. The tissue response depends on the receptors it bears. You may find the following principles useful:

1. Autonomic effector cells may possess α- and β-, or only β-adrenoceptors, in addition to ACh receptors.
2. α receptors dominate over β receptors.
3. α receptors cause smooth muscle contraction [except intestinal SM]; β receptors cause relaxation [except cardiac muscle].
4. β receptors generally stimulate secretion; α receptors inhibit it.
5. Where β receptors cause SM relaxation, ACh causes contraction.
6. Where α receptors cause SM relaxation, ACh causes relaxation.

- **Intermediary metabolism.** ***Carbohydrate.*** Blood glucose is elevated, as adrenaline stimulates hepatic glycogenolysis and glucose release (α, β) as well as glycogenolysis [glycogen→lactic acid] in skeletal muscle (β). This lactic acid is a substrate for hepatic gluconeogenesis. Catecholamines inhibit insulin secretion (α) and stimulate glucagon secretion (β). ***Fat.*** Lipolysis is promoted in adipose tissue (β), resulting in FFA formation; brain and cardiac muscle can use FFAs as a direct energy source to spare glucose, or they can be used by the liver to make glucose. ***Protein.*** Adrenaline reduces proteolysis in skeletal muscle (β). This makes sense: in a "fight or flight" situation you want your muscles intact.
- **Thermogenesis.** In rats, overfeeding stimulates the SNS, and fasting depresses it. Piloerection is caused by the SNS. Adrenaline stimulates brown adipose tissue (BAT) which generates heat; this is important in babies, who cannot shiver; its significance in adult humans is unclear.
- **Cardiovascular system.** Adrenaline increases cardiac force and heart rate (β). Blood is shunted away from the skin, mucosa, connective tissue and kidneys (α). Skeletal muscle and coronary arteries have β receptors, so their blood supply remains good. The decreased renal blood flow reduces glucose clearance, and this may be responsible for the prolonged hyperglycaemia caused by catecholamines.[3]
- **Respiratory system.** Bronchial smooth muscle is relaxed (β), dilating the bronchial tree.
- **The Stress Response.** The sympathetic NS/adrenal medulla provide a general "fight/flight" endocrine reaction.

[2] Cheese 'n' wine effect – MAO inhibitors are used as antidepressants. If you then eat tyramine-rich foods (cheese, chocolate, Marmite, Chianti) the tyramine can then reach the circulation without being broken down by gut MAO and cause acute hypertension which can cause strokes.
[3] I know this sounds odd; the kidneys aren't supposed to clear glucose; this is a case of "Hadley says so".

Cushing's syndrome (chronic excess of cortisol)

Causes

1. prolonged exogenous glucocorticoid [iatrogenic]
2. pituitary hypersecretion of ACTH (Cushing's *disease*), usually due to an adenoma
3. ectopic production of ACTH or CRH by a non-endocrine neoplasm
4. hypersecretion of cortisol by an adrenal neoplasm (ACTH-independent)

The commonest manifestations

central obesity (trunk, upper back)
"moon face, buffalo hump"
weakness, fatigue
hirsutism
hypertension, fluid retention
plethora
glucose intolerance/diabetes ("steroid diabetes")
osteoporosis
psychiatric abnormalities (esp. depression)
menstrual abnormalities
gastric acidity, peptic ulcers
skin striae

Primary hyperaldosteronism

Common causes

- Solitary aldosterone-secreting adenoma: **Conn's syndrome** (65%)
- Bilateral idiopathic hyperplasia of adrenals (30%)

Liquorice causes *apparent* mineralocorticoid excess because it inhibits the enzyme responsible for the peripheral cortisol→cortisone shunt, thus rendering mineralocorticoid-sensitive tissues (kidney) sensitive to circulating glucocorticoids (cortisol) as well.

Effects

↓ renin
hypokalaemia
sodium retention
hypertension

The ↑ECFV and ↓K^+ can cause heart failure.

Treatment

spironolactone (= aldosterone antagonist)

Adrenocortical insufficiency – primary, acute

- includes insufficiency due to rapid withdrawal of exogenous steroids
- also adrenal haemorrhage (in the setting of sepsis, called the Waterhouse-Friderichsen syndrome)
- effects: see below

Adrenocortical insufficiency – primary, chronic (Addison's disease)

Destruction of cortex (often autoimmune) results in deficiency of both glucocorticoids and mineralocorticoids.

- **Glucocorticoid lack:** Weakness, fatigue, anorexia, nausea, vomiting, weight loss, hypotension…
- **Aldosterone lack:** hyperkalaemia, hyponatraemia, hypotension
- **ACTH excess:** hyperpigmentation of the skin (because ACTH is raised – the pituitary tries to compensate – and ACTH resembles MSH enough to stimulates melanocytes to produce pigment).
- **Death from:** hyperkalaemic cardiac arrhythmias, cerebral hypoglycaemia ("Addisonian crisis")

Adrenocortical insufficiency – secondary

Due to lack of ACTH. Cortisol is deficient, but androgens and aldosterone are near normal (not dependent on ACTH).

Phaeochromocytoma

Just so you don't think the medulla is immune to disease… A phaeochromocytoma (adrenal chromaffin tumour) is a benign tumour that secretes catecholamines – effects include severe hypertension, weight loss, tremor, hyperventilation and myocardial infarction.

Most general physiology textbooks cover endocrinology reasonably well.
For more detail, try Hadley (1992), *Endocrinology (third edition)*.