Endocrine system 4: adrenal glands

Key points

There are two adrenal glands: one located above each kidney

Adrenal glands consist of two parts, the cortex and the medulla, which each produce different hormones

The adrenal cortex produces a diverse range of steroid hormones, using cholesterol as a substrate

The main hormones produced by the medulla are the ‘flight or fight’ hormones adrenaline and noradrenaline

Endocrine functions of the adrenal glands

Hormones of the adrenal glands

The role of adrenal gland hormones in mediating essential physiological processes

This eight-part series on the endocrine system opened with an overview of endocrine glands and the role of hormones as chemical signals that help maintain the homeostatic balance that is essential to good health. This fourth article examines the anatomy and physiology of the adrenal glands.

Anatomy

There are two adrenal (suprarenal) glands: one located immediately above each kidney (Fig 1). They are yellow to orange in colour and are positioned retroperitoneally (behind the peritoneal membrane lining the abdominal cavity). The right adrenal gland is at, approximately, the level of the 12th rib, while the left is located slightly higher between the 11th and 12th ribs (Perrier and Boger, 2005).

Normal, healthy adult adrenal glands are relatively small – they each weigh 4-6g, and are around 3cm wide, 5cm high and 1cm thick; changes in size are often indicative of underlying pathology (Lack and Paal, 2019; Westphalen and Bonnie, 2006).

The right adrenal gland is usually distinctly triangular in appearance, resembling a witch’s hat, while the left is more flattened and typically crescent shaped.

The adrenals are highly vascularised, and each gland is supplied with oxygenated blood through superior, middle and inferior suprarenal arteries; deoxygenated blood is carried away from each gland via an adrenal vein (Perrier and Boger, 2005).

Internal structure

Each adrenal gland is protected by a thick collagen-rich outer capsule, with glandular tissues located beneath. The largest portion is the outer region, called the adrenal cortex, accounting for around 90% of total adrenal volume (Gorman, 2013).
The adrenal cortex produces a diverse range of steroid hormones, using cholesterol as a substrate. These include the long-term stress hormone cortisol, aldosterone (regulating levels of sodium and potassium in the blood) and a group of testosterone-like hormones called androgens.

The adrenal medulla is the inner region of the adrenal gland, accounting for around 10% of adrenal volume (Gorman, 2013), and produces adrenaline (epinephrine) and noradrenaline (norepinephrine). These have diverse physiological effects, but function primarily to activate the sympathetic branch of the autonomic nervous system (ANS) and prepare the body for immediate action (VanPutte et al, 2017).

**Adrenal medulla**
The major cells of the adrenal medulla are called chromaffin cells because they take up stains containing chromium salts (Mubarik and Aeddula, 2021). Chromaffin cells produce amino acid-derived hormones called catecholamines.

**Adrenaline and noradrenaline**
The two major catecholamines are adrenaline (epinephrine) and noradrenaline (norepinephrine), which are enzymatically derived from the amino acid tyrosine. These are commonly referred to as the ‘fight-or-flight’ hormones, and will be explored later in this article.

Tyrosine is a non-essential amino acid that can be obtained through diet or derived from the essential amino acid phenylalanine. Chromaffin cells continually take up tyrosine and, through the sequential actions of several enzymes, convert it into the active catecholamines L-dopa, dopamine, noradrenaline and adrenaline. Tyrosine is also taken up by the neurons in the ANS to generate noradrenaline, which functions as a key neurotransmitter in the sympathetic branch of the ANS.

In the adrenal medulla, adrenaline is the major product of catecholamine biosynthesis, accounting for around 95% of the medullary hormones released into the blood (Berends et al, 2019).

**Fight-or-flight response**
When we perceive a threat (for example, by a predator) or are in a potentially dangerous or exciting situation (for example, at the top of a bungee jump), adrenaline and smaller amounts of noradrenaline are usually released. The bulk of noradrenaline in the circulation is derived from the sympathetic nerve endings because the sympathetic branch of the ANS is activated in acutely stressful situations. The adrenal medulla itself is innervated with sympathetic nerve endings that, when activated, initiate the release of more adrenaline, further amplifying the fight-or-flight response (Verberne et al, 2016).

Adrenaline and noradrenaline have multiple and diverse physiological effects that prepare the body for immediate action. The most obvious effects of the sudden release of catecholamines (adrenaline rush) primarily centre on the cardiovascular system. Adrenaline binds to beta-adrenergic receptors associated with the sinoatrial node (SAN) of the heart (Macdonald et al, 2020). The SAN functions as the heart’s natural pacemaker and adrenaline dramatically accelerates the heart rate, often way beyond the upper limit for normal resting heart rate of 100 beats per minute (bpm). This is often perceived as a notable thumping in the chest and, as cardiac output and blood pressure increase, the pulse may be perceived (without palpation) in other areas of the body, such as the neck and temples.

Adrenaline also further increases blood pressure by promoting vasoconstriction in the skin and gastrointestinal tract, hence the expression of skin turning ‘ashen with fear’ and the common sensation of ‘butterflies in the stomach’. Simultaneously, adrenaline promotes vasodilation of the arteries in the skeletal muscles and coronary circulation, diverting oxygenated blood to the major muscle groups and myocardium of the heart. Adrenaline improves oxygen uptake by dilating the airways and increasing the breathing rate, increasing blood glucose, and improving sensory perception and response times while decreasing the perception of pain (VanPutte et al, 2017). Cumulatively, this enhances musculoskeletal function, so an individual can put up an effective fight or escape any potential threat (Table 1).

The effects of adrenaline and noradrenaline are rapid and usually observed within a few seconds of release; the primary effect of adrenaline in accelerating heart rate ensures its rapid distribution throughout the body. Adrenaline is a short-acting hormone with a half life of around 2-3 minutes; it is rapidly metabolised by the liver and excreted in the urine (Electronic Medicines Compendium, 2020).

**Adrenal cortex**
The adrenal cortex lies immediately below the protective collagenous adrenal capsule and continually takes up cholesterol as the substrate to generate a diverse range of steroid hormones. Histologically, the cortex consists of three distinct layers of tissue, each producing its own class of steroid hormones:

- **Zona glomerulosa (outer layer)** – synthesises mineralocorticoids that help regulate electrolyte concentrations;
- **Zona fasciculata (middle layer)** – synthesises glucocorticoids that primarily function as long-term stress hormones;
- **Zona reticularis (inner layer)** – marks the boundary between the cortex and the medulla, producing a class of testosterone-like hormones called androgens.

**Aldosterone**
As their name suggests, the mineralocorticoid hormones produced by the zona glomerulosa regulate plasma concentrations of minerals/salts (electrolytes). The most important mineralocorticoid in humans is aldosterone, which regulates blood concentrations of ionic sodium (Na+) and ionic potassium (K+). Na+ and K+ ions are essential for maintaining membrane potentials and generating nerve impulses (action potentials),
Aldosterone acts on the kidneys to stimulate reabsorption of salt (NaCl) and water (H2O). This ensures that most Na+ ions are concentrated in the intracellular fluid, while most K+ ions are found in the extracellular fluids, with large amounts accumulating in the blood plasma, while most K+ ions are concentrated in the intracellular fluid.

Although this mechanism ensures the correct distribution of Na+ and K+ between the intracellular and extracellular compartments of the body, it is aldosterone that fine tunes the plasma concentration of Na+ and K+. In health, the normal plasma concentration of Na+ is maintained at 135-145 mmol/l, while the activity of the sodium-potassium pump keeps plasma concentration of K+ much lower at 3.5-5.0 mmol/l (Justice et al, 2019).

Aldosterone is released in response to hyponatraemia (low blood sodium), most commonly due to a lack of Na+ in the diet or Na+ loss through sweating. Aldosterone increases and normalises plasma Na+ concentrations by several mechanisms:

- Enhancing the reabsorption of Na+ into the blood from the renal filtrate at the distal convoluted tubule and collecting duct of kidney nephrons;
- Promoting salt cravings to encourage consumption of potassium-rich foods or food supplements, such as bananas or low-sodium salt replacements containing potassium chloride. Hyperkalaemia can also follow major physical injury causing disruption of cell membranes (for example, a burn), leading to the release of large amounts of intracellular potassium that have accumulated via the Na+ K+ pump (Ookuma et al, 2015).
- Reducing loss of Na+ in sweat, saliva and pancreatic juice (Byrd et al, 2018; VanPutte et al, 2017).
- Conversely, aldosterone secretion reduces in response to hyperkalaemia (high blood potassium), most commonly following consumption of potassium-rich foods or food supplements, such as bananas or low-sodium salt replacements containing potassium chloride. Hyperkalaemia can also follow major physical injury causing disruption of cell membranes (for example, a burn), leading to the release of large amounts of intracellular potassium that have accumulated via the Na+ K+ pump (Ookuma et al, 2015).
- Aldosterone reduces and normalises the blood-potassium concentration, primarily by promoting the excretion of K+ ions into the kidney nephrons for elimination in the urine.

**Hyperkalaemia and hypokalaemia**

Aldosterone also regulates concentration of plasma K+ ions and is released in response to hyperkalaemia (high blood potassium), most commonly following consumption of potassium-rich foods or food supplements, such as bananas or low-sodium salt replacements containing potassium chloride. Hyperkalaemia can also follow major physical injury causing disruption of cell membranes (for example, a burn), leading to the release of large amounts of intracellular potassium that have accumulated via the Na+ K+ pump (Ookuma et al, 2015).

Severe hyperkalaemia requires urgent assessment, as it can interfere with the electrical conductive tissues of the heart, leading to dangerous ventricular arrhythmias and, potentially, cardiac arrest (Weiss et al, 2017). Aldosterone reduces and normalises the blood-potassium concentration, primarily by promoting the excretion of K+ ions into the kidney nephrons for elimination in the urine.

**Blood pressure regulation**

The primary stimulus for aldosterone release is the activation of the renin angiotensin aldosterone system (RAAS) (Byrd et al, 2018). The RAAS is the most important physiological mechanism for medium to long-term control of blood pressure and is centred around a plasma protein called angiotensinogen, produced by the liver (Atlas, 2007). When the kidneys detect a drop in blood pressure, they produce the enzyme renin, which converts angiotensinogen into an inactive protein called angiotensin I. This circulates in the plasma until it reaches the lung tissue, where angiotensin-converting enzymes (ACE) convert it into biologically active angiotensin II. This primarily functions as a vasoconstrictor, helping to restore blood pressure while simultaneously stimulating the release of aldosterone from the adrenal cortex.

Aldosterone promotes the reabsorption of Na+ in the kidney, thereby increasing plasma Na+ concentration (Fig 2). This encourages the movement of water from the tissues into the blood vessels by osmosis, thereby increasing blood volume and blood pressure.

Hyperkalaemia can result from a lack of potassium in the diet or a side-effect of some diuretic medications. Diuretics such as furosemide are used to reduce oedema and treat high blood pressure by eliminating excess fluids and blood volume through increasing urine output; however, this can lead to significant flushing out of K+. Hyperkalaemia inhibits aldosterone secretion, reducing the secretion of K+ in the renal filtrate and causing the retention of K+ in the blood.

Newer forms of potassium-sparing diuretics are available, such as amiloride or triamterene, which increase urine output with minimal loss of K+ (Bit.ly BNFDiuretics).
Primary aldosteronism

Primary aldosteronism (PA, also known as Conn’s syndrome) is a condition that is most often caused by benign enlargement (hyperplasia) of the adrenal glands or by tumours in the adrenal cortex. It leads to excess secretion of aldosterone, causing hypernatraemia, which increases blood volume and blood pressure. Around 5-10% of cases of hypertension are thought to be caused by PA (Young, 2019).

Patients with PA also usually show hypokalaemia as increased aldosterone promotes the rapid secretion of potassium in the urine. Other signs and symptoms include water retention and neurological/psychological symptoms, including anxiety, demoralisation, stress, depression and nervousness. When PA is caused by tumours, surgery is usually the treatment of choice; excess aldosterone secretion caused by adrenal hyperplasia is usually treated using aldosterone-blocking drugs (Young, 2019).

Androgens

The zona reticularis secretes small amounts of hormones called androgens, which are structurally similar to the male sex hormone, testosterone. Like testosterone, these hormones function as anabolic steroids of varying potency and promote the development of male physical characteristics such as increased muscle mass, growth of body and facial hair, and deepening of the voice. In females, androgens play key roles in the functioning of the musculoskeletal system, heighten libido and form intermediates and deepening of the voice. In females, androgens play key roles in the functioning of the musculoskeletal system, heighten libido and form intermediates.

Androgens, including synthetically produced testosterone, are of clinical use in people physically transitioning from female to trans male, as they help ensure a match between gender identity and physical body (gender congruence). Such masculinising hormone therapy, also known as gender-affirming hormone therapy, helps to block the activity of female sex hormones, such as oestrogens, and suppress the normal menstrual cycle (Bit.ly/PFCushings). Most cases of CS are caused by benign pituitary tumours leading to excess secretion of ACTH, which increases secretion of cortisol from the zona fasciculata. More rarely, hypersecretion of cortisol may be caused by adrenal tumours, this uncommon form is referred to as adrenocortical Cushing’s (Pappachan et al, 2017).

Cushing’s syndrome

Cushing’s syndrome (CS) or hypercortisolism is characterised by increased secretion of cortisol. It is more prevalent in women than men and, although it can occur at any age, is most commonly detected at 30-40 years. It is relatively rare, with a reported incidence of around 1 in 200,000, but appears to be becoming more common (Bit.ly/PFCushings).
Clinical Practice
Systems of life

...can lead to muscle wastage and thin, stick-like arms and legs.

A major characteristic of CS is abnormal fat distribution, with increased central-trunk obesity leading to large accumulations of abdominal fat, increased fat around the face (moon face) and possible prominent fat between the shoulder blades (buffalo hump). Excess cortisol is also associated with a thinning of the skin, causing it to bruise easily, and prominent striae (stretch marks), particularly in areas of rapid fat deposition, such as the abdomen. Other common symptoms are fatigue, poor concentration and memory, decreased libido and loss of bone density, potentially leading to osteoporosis (Nieman et al, 2008). How to treat CS depends on the cause but surgical excision of tumours at the pituitary or adrenal glands is usually the treatment of choice.

Addison’s disease

Addison’s disease (AD) affects around 1 in 10,000 people (Bit.ly/ADSHGAddisons) and is characterised by the reduced secretion of hormones from the adrenal cortex. It is usually associated with depletion in all three categories of adrenal steroid hormones (mineralocorticoids, glucocorticoids and androgens). There are many known causes of AD, with autoimmune destruction of the tissues of the adrenal cortex the most common in developed countries (Michels and Michels, 2014). The depletion of aldosterone and cortisol after damage to the zona glomerulosa and zona fasciculata precipitates many of the symptoms associated with AD.

AD onset is usually insidious and often goes unrecognised for long periods. Symptoms are incredibly diverse, hindering diagnosis, particularly in the disease’s early stages. As the reduced secretion of the hormones of the adrenal cortex will activate the HPA axis, AD is usually associated with increased levels of ACTH. Part 2 of this series highlighted that ACTH is structurally similar to melanocyte-stimulating hormone, which can lead to hyperpigmentation in areas of skin – a common feature of AD. The most common symptoms can usually be traced back to a lack of aldosterone, cortisol or both as highlighted below:

- Lethargy, drowsiness and overwhelming exhaustion – lack of cortisol and aldosterone;
- Loss of appetite, nausea and unintentional weight loss – lack of cortisol and aldosterone;
- Hypotension and postural hypotension – lack of aldosterone;
- Hyperpigmentation, leading to dark patches of skin – increased ACTH;
- Hypoglycaemia – lack of cortisol;
- Hyponatraemia and hyperkalaemia – lack of aldosterone;
- Muscle weakness and cramping – lack of aldosterone;
- Polyuria and increased thirst – lack of aldosterone;
- Low mood or irritability – lack of cortisol and aldosterone;
- Increased thirst – lack of aldosterone (Bit.ly/NHSAddisons).

Treatment and management of AD is usually achieved through life-long synthetic hormone replacement therapy with glucocorticoids (cortisone or hydrocortisone) and mineralocorticoids (fludrocortisone) (Bornstein et al, 2016).

Severe deficiency of aldosterone and cortisol can be life-threatening and lead to a medical emergency termed an adrenal crisis. This is characterised by some or all of the following symptoms:

- Rapid shallow breathing;
- Severe dehydration;
- Sweating;
- Pale, cold, clammy skin;
- Dizziness;
- Hypotension;
- Severe vomiting and diarrhoea;
- Abdominal pain or pain in the side;
- Fatigue and severe muscle weakness;
- Headache;
- Severe drowsiness or loss of consciousness (Bit.ly/NHSAddisons).

Unless treated quickly, adrenal crisis can lead to convulsions, coma and death; it is usually treated with intravenous hydrocortisone (Bornstein et al, 2016).

Conclusion

This article has explored the anatomy, physiology and function of the adrenal glands. Part 5 will focus on the pineal and thymus glands. NT

References


