

## THE ADRENAL GLANDS

### ANAESTHESIA TUTORIAL OF THE WEEK 216 7<sup>th</sup> MARCH 2011

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### QUESTIONS

Before reading the tutorial answer the following true/false questions:

Q1.

- a. The adrenal glands consist of an inner medulla and outer cortex.
- b. The medulla produces mainly catecholamines.
- c. The cortex produces mainly catecholamines.
- d. The zona glomerulosa produces aldosterone.
- e. The zona fasciculata produces androgens.

Q2.

- a. Tyrosine is the precursor for catecholamines.
- b. Epinephrine is the precursor of norepinephrine.
- c. Aldosterone causes sodium and water retention.
- d. Cortisol inhibits gluconeogenesis.
- e. The zona reticularis produces sex hormones.

Q3. Pheochromocytoma:

- a. Arises from the adrenal medulla.
- b. Is bilateral in 10% of patients.
- c. Causes paroxysms of hypotension.
- d. May present initially with symptoms of myocardial ischemia.
- e. Can be diagnosed by measuring plasma norepinephrine.

Q4. Cushing's disease:

- a. Is caused by an adrenal adenoma.
- b. Causes progressive weight loss.
- c. May cause amenorrhea.
- d. May present with symptoms of diabetes mellitus.
- e. Is diagnosed using a dexamethasone suppression test.

Q5. Addison's disease:

- a. Is due to failure of the adrenal medulla.
- b. Is associated with increased pigmentation.
- c. Causes progressive weight loss.
- d. Causes low plasma ACTH levels.
- e. Will require treatment with increased steroids peri-operatively.

## INTRODUCTION

Homeostasis or maintenance of the body's internal environment is a complex process of interconnected pathways and feedback loops. One of the major links in a number of these pathways is the adrenal gland. The adrenals compared to the body as a whole are small but they produce some major hormones and as such, medical conditions arising from them often have profound effects on the body.

Knowledge of these conditions, an understanding of their role and subsequent pathology is vital to the treatment of patients undergoing surgery.

## ANATOMY OF THE ADRENAL GLANDS

### Relations

The adrenal glands (figure 1) are an important organ but often overlooked as a single entity due, most likely, to their size and position in the body. They are located behind the abdominal cavity and peritoneum in the retroperitoneal space, one on the superior pole of each kidney hence they are often referred to as the "suprarenal glands". They are surrounded by renal fascia and adipose tissue and are obedient factories producing essential hormones for the body.

### Blood Supply

The arterial blood supply to each adrenal gland is via three adrenal arteries:

The superior suprarenal artery, a branch of the inferior phrenic artery

The middle suprarenal artery, a branch of the aorta

The inferior suprarenal artery, a branch of the renal artery.

The venous drainage of the adrenal glands is via the suprarenal veins which drain into different main veins on each side:

- the *right* into the **inferior vena cava**
- the *left* into either the **left renal** or **left inferior phrenic vein**.

### Nerve supply

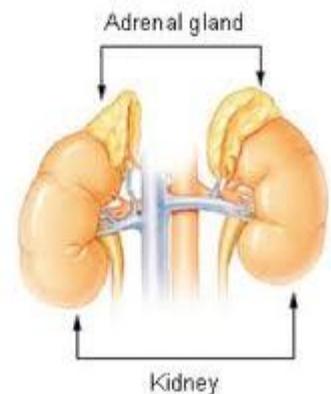
As an organ of hormone production the adrenals have a rich nerve supply. Branches from the coeliac plexus and the thoracic splanchnic nerves supply the chromaffin cells of the medulla (see below).

### Functional anatomy

The adrenal gland can be divided into two very distinct zones, each of which produces specific hormones:

- The inner part of the adrenal or **medulla** produces and secretes **amine** hormones, adrenaline (epinephrine) and noradrenaline (norepinephrine). The medulla is essentially a sympathetic ganglion where the postganglionic cells have become secretory cells named chromaffin cells (also called phaeochromocytes – see below).
- The outer part of the adrenal gland or **cortex** makes up the majority of the gland. Three main types of hormones are secreted; mineralocorticoids, glucocorticoids, and androgens. Each is produced in a different part of the cortex
  - the outer **zona glomerulosa** producing mainly the mineralocorticoid aldosterone
  - the middle **zona fasciculata** producing glucocorticoids eg cortisol
  - the innermost layer the **zona reticulosa** producing androgens.

These zones are remembered as G.F.R. and as they sit on top of the kidneys, this is a handy *aide memoire*.



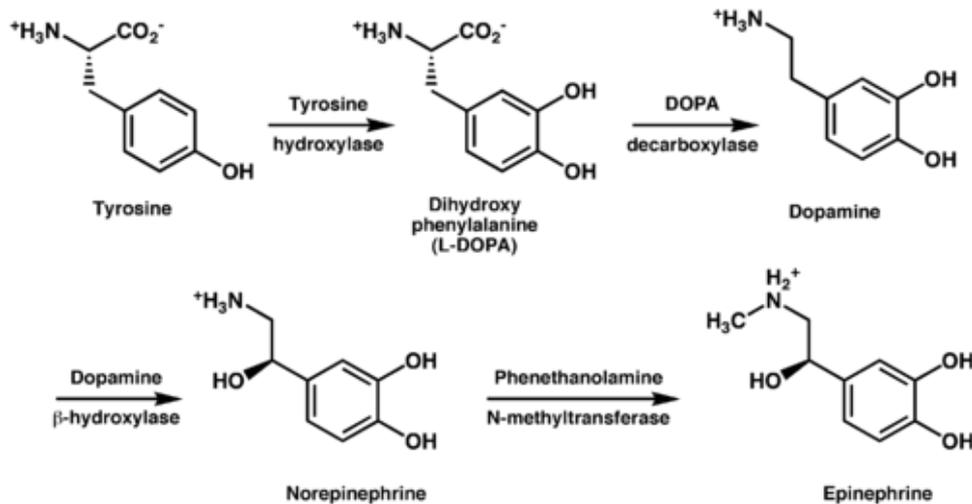
**Figure 1.** The Adrenal gland (Reproduced with permission from the Internet Encyclopedia of Science)

## BIOCHEMISTRY AND PHYSIOLOGY OF THE ADRENAL HORMONES

### Medullary hormones

- Amines : adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine
- Others: acetylcholine, metenkephalin, chromogranin A

The amines are produced from phenylalanine or tyrosine and are often referred to as “catecholamines” which reflects their structure; they contain a catechol (a benzene ring with hydroxyl groups at positions 1 and 2, or 1,2 dihydroxybenzene and an amine side chain). The synthesis of these hormones is shown in figure 2.



**Figure 2:** Catecholamine synthesis

Both adrenaline and noradrenaline have different degrees of action on adrenergic receptors (termed alpha and beta adrenoreceptors), both essentially part of the bodies primeval ‘fight or flight’ stress response with actions mainly on the cardiovascular and respiratory system; increased alertness, dilatation of the bronchioles, increased heart rate and contractility and changes in metabolism to favour release of energy.

#### Alpha( $\alpha$ ) adrenoreceptors

These are subdivided into:

$\alpha$  1 - responsible for vascular smooth muscle contraction, i.e. control of the degree of vasoconstriction in the skin, gut and kidneys. Stimulated glycogenolysis and gluconeogenesis. Relaxes the pregnant uterus.

$\alpha$  2 - responsible for platelet activation (increased adhesiveness) and synaptic transmission. Inhibits insulin release, stimulates glucagon release.

#### Beta( $\beta$ ) adrenoreceptors

These are subdivided into:

$\beta$  1 - increases the rate (positively chronotropic) and force of contraction (positively inotropic) of the heart. Increases renin secretion.

$\beta$  2 – smooth muscle relaxation i.e. dilatation of bronchioles and blood vessels in skeletal muscle. Stimulated glycogenolysis and gluconeogenesis. Increases insulin secretion from beta cells of the pancreas. Increases renin secretion.

Dopamine is mainly a neurotransmitter and does not cross the blood brain barrier. As such it is produced and has its effects locally. Exogenous dopamine is, however, used in clinical practice as it is an agonist to peripheral dopamine (D),  $\beta$  and  $\alpha$  receptors. The effects are dose related; initially only dopamine receptors are stimulated followed by action upon  $\beta$  and then  $\alpha$  adrenoreceptors. Dopamine receptors are located in renal arterioles and their stimulation causes renal vasodilatation. It has been used in low dose infusions to maintain renal perfusion if compromised in clinical states although its efficacy is questionable.

## Cortical hormones

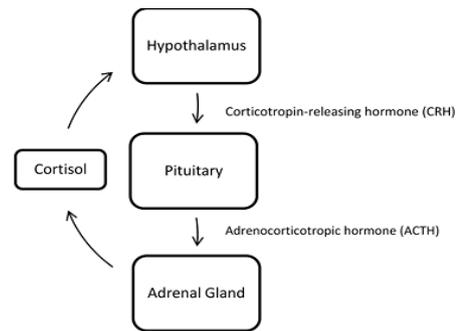
All the adrenal cortical hormones are produced from the common precursor cholesterol.

### *Zona glomerulosa*

This region of the adrenal cortex produces aldosterone, a mineralocorticoid. Its release is the end point of the renin-angiotensin-aldosterone system. This system plays an important role in regulating blood volume and systemic vascular resistance, which together influence cardiac output and blood pressure. The main action of aldosterone is to retain sodium in the kidneys (in exchange for potassium) which in turn causes fluid retention. Aldosterone can be released by the renin-angiotensin system, but also by ACTH, following physiological stress or trauma, hyperkalemia and directly by hyponatraemia.

### *Zona fasciculata*

This region of the cortex produces cortisol. Its main action is on gluconeogenesis and as such, it is termed a glucocorticoid. However, mineralocorticoid activity may be seen in conditions associated with excess secretion (see below). Cortisol has a major function in response to stress and suppressing the immune system. It also maintains levels of glucose in the blood by stimulating gluconeogenesis and regulates the metabolism of proteins, carbohydrates, and fats. Its release is under the control of the hypothalamic-pituitary axis in response to the production of adrenal corticotrophic hormone (ACTH). Cortisol has a diurnal variation with the peak at 8am, is essential for life and has a multitude of actions.



**Figure 3:** Regulation of cortisol production

The synthetic production of cortisol and other corticosteroids is one of the major advancements in medical science and had allowed us to suppress immunological and inflammatory processes. Steroids are used to treat a plethora of ailments from asthma, dermatological conditions to allowing transplanted organs to survive.

### *Zona reticulosa*

This region of the adrenal cortex and is named due to the reticular or net like appearance it has microscopically and it produces dehydroepiandrosterone (DHEA), and androstenedione. These are weak androgenic (sex) hormones but are converted into the more potent testosterone and oestrogens in the testes and ovaries respectively. The release of these hormones is controlled by ACTH and they are responsible for protein anabolism and growth.

## MEDICAL CONDITIONS ASSOCIATED WITH ABNORMALITIES OF THE ADRENAL GLAND

Hormone	Syndrome	Features
Catecholamines	phaeochromocytoma	Hypertension, Flushing, abdominal cramps, palpitations headaches.
Glucocorticoid excess	Cushing's syndrome	Buffalo hump, Moon face, truncal obesity, abdominal striae, muscle weakness and wasting, hypertension, diabetes mellitus, hypokalaemia and metabolic alkalosis.
Adrenocortical insufficiency	Addison's disease	Skin pigmentation, Na <sup>+</sup> depletion, fatigue, lethargy muscle weakness, low mood (mild depression) or irritability, loss of appetite and unintentional weight loss, hypotension.
Mineralocorticoid excess	Conn's syndrome	K <sup>+</sup> depletion, Na <sup>+</sup> retention, polyuria and hypokalaemic alkalosis, hypertension, tetany and weakness.
Adrenal androgen excess	adrenogenital syndrome adrenal congenital hyperplasia	<i>In female:</i> hirsutism, acne, oligomenorrhea & virilisation. <i>In male:</i> precocious puberty

### Adrenal medulla - phaeochromocytoma

A phaeochromocytoma is a tumour that arises in the adrenal medulla and secretes catecholamines. In 1912 the German pathologist Pick coined the term "phaeochromocytoma" from the Greek 'phaios' (dusky) and 'chromo' (colour). It is known as "the 10% tumour" because:

- 10% are bilateral
- 10% arise outside the adrenals
- 10% are malignant
- 10% are familial

It has a wide range of symptoms depending on the catecholamine secretion:

- Hypertension, often paroxysmal. Complications of this may be the first signs e.g. stroke, myocardial infarction
- Attacks of:
  - Palpitations
  - Pallor, flushing and sweating
  - Tremor
  - Headaches
  - Anxiety
- Abdominal pain, nausea and/or vomiting
- Weight loss
- Constipation or diarrhoea
- Glucose intolerance

### Diagnosis

24 hour urinary collection. Measuring the excretion of metanephrines (breakdown product) or free catecholamines. Occasionally plasma norepinephrine (noradrenaline) is measured. Localisation is usually by CT scanning.

### Anaesthesia

Specialist anaesthetic considerations have to be observed in surgical removal of phaeochromocytomas as handling these tumours can cause a surge of catecholamine release, severe hypertension and end

organ damage. Preoperatively patients are given a non-selective alpha antagonist (alpha 1 and 2) traditionally phentolamine. Once alpha blockade is achieved then beta blockade is started to counter the increase in cardiac output due to the alpha 2 blockade. A more selective approach using doxazosin (alpha 1 blockade) has the benefit of not requiring the beta blockade. However, there is always the risk that a large release of catecholamines from the tumour during surgery may overcome the block causing increased instability. More details can be found at ANAESTHESIA TUTORIAL OF THE WEEK 151.

### **Adrenal cortex. Zona glomerulosa - primary hyperaldosteronism (Conn's syndrome)**

Primary hyperaldosteronism was first described by Conn in 1955. An overproduction of aldosterone causes sodium retention which in turn leads to:

- hypertension
- headaches
- muscle cramps, due to the low potassium (may be exacerbated by the treatment of the "hypertension" with thiazide diuretics)
- metabolic alkalosis, due to increased secretion of H<sup>+</sup> ions by the kidney

The high pH of the blood makes calcium less available to the tissues and causes symptoms of hypocalcaemia.

- Paraesthesia (usually fingers, toes and around mouth)
- Tetany
- Carpopedal spasm (wrist flexion)
- Muscle cramps

Note: liquorice (glycyrrhizin) ingestion can mimic the symptoms!

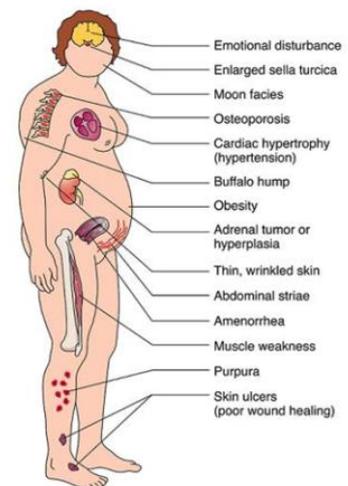
### **Diagnosis**

Persistent hypernatraemia, hypokalaemia and metabolic alkalosis in the absence of the use of diuretics therapy is very suggestive. Confirmation in many cases may be made by measuring plasma or urinary aldosterone and renin levels and the ratio of these two hormones.

### **Adrenal cortex. Zona fasciculata- Hypercortisolism (Cushing's syndrome)**

Cushing's syndrome, first described by Harvey Cushing in 1932, is a collection of signs and symptoms associated with prolonged, raised levels of glucocorticoid in the blood. The cause may be endogenous e.g. adrenal cortical adenoma or exogenous e.g. therapeutic use of prednisolone (non-ACTH dependent). Cushing's disease refers specifically to a state of high cortisol caused by an adenoma in the pituitary gland which releases an excess of ACTH (80% cases) and more rarely an ACTH secreting tumour e.g. small cell carcinoma of the bronchus (ACTH-dependent). The signs of the syndrome are not unfamiliar to anyone who has seen patients on long-term steroids and gives rise to the characteristic features: fat pads on the upper back (buffalo hump) and face (moon face), weight gain centrally (centripetal obesity), striae on the trunk, thin legs, and excess facial hair. Patients are often described as a "lemon on matchsticks". In addition long term cortisol causes:

- change of appearance
- depression, psychosis
- insomnia
- amenorrhoea/oligomenorrhoea
- poor libido
- thin skin/easy bruising
- hair growth/acne
- muscular weakness
- growth arrest in children
- back pain
- polyuria/polydipsia.



**Figure 4:** Features of Cushing's syndrome.

These signs can also be remembered by the mnemonic:

**C** - Central obesity, Cervical fat pads, Collagen fibre weakness, Comedones (acne)

**U** - Urinary free cortisol and glucose increase

**S** - Striae, Suppressed immunity

**H** - Hypercortisolism, Hypertension, Hyperglycaemia, Hirsutism

**I** - Iatrogenic (Increased administration of corticosteroids)

**N** - Non-iatrogenic (Neoplasms)

**G** - Glucose intolerance, Growth retardation

### *Diagnosis*

Low-dose dexamethasone suppression test. Following the collection of baseline urine samples to measure cortisol levels, dexamethasone 0.5mg is taken orally every six hours (precisely) for two days. 24-hour urine collections are performed on the second day of medication and the day after stopping (day 3). Alternatively, plasma cortisol levels can be measured before and after treatment. In normal patients, low-dose dexamethasone stops cortisol being produced and urine and plasma levels fall. In Cushing's syndrome, production of cortisol is maintained and levels remain high confirming the diagnosis.

### **Primary hypocortisolism (Addison's disease)**

Thomas Addison first identified the disease in 1855. It is caused by a failure of the adrenal cortex due to an autoimmune process, infection or surgery. Addison's disease is not usually apparent until over 90% of the adrenal cortex has been destroyed, so that very little adrenal capacity is left.

Symptoms are those of:

- fatigue /lethargy
- muscle weakness
- low mood (mild depression) or irritability
- loss of appetite and unintentional weight loss
- hypotension
- polyuria
- increased thirst
- craving for salty foods
- hypoglycaemia

All of these symptoms may occur in a rather insidious nature and as such make it difficult to diagnose. It usually intercurrent trauma or infection requiring an increase in steroid production that unmask the problem. The lack of cortisol fails to feedback to the pituitary and so there is continual production of ACTH to attempt to stimulate cortisol production. Consequently ACTH levels are high. Melanocyte stimulating hormone (MST) is also released in conjunction and leads to the characteristic pigmentation of the skin and buccal mucosa seen in Addisonian patients.

### *Diagnosis*

A Synacthen Stimulation Test is often used to aid diagnosis. Synacthen is the trade name for tetracosactide, a synthetic ACTH analogue. When synacthen is given, the adrenal glands normally respond in the same way as they would to ACTH and increase plasma cortisol and aldosterone levels. However, if the ACTH level is high, but the cortisol and aldosterone levels are low, it is usually confirmation of Addison's disease.

### *Addisonian crisis and anaesthesia*

Adrenal crisis is a life-threatening condition which can be induced by stress during surgery in patients with adrenal insufficiency. Exogenous replacement should be considered in such cases, this includes all patients on long term steroids as they will also display iatrogenic adrenal suppression.

### **Secondary hypocortisolism (pituitary tumour, Sheehan's syndrome)**

This is caused by reduced levels of ACTH production following damage to the anterior pituitary. In this situation there is a deficiency in both mineralocorticoids and glucocorticoids. Mineralocorticoid deficiency leads to loss of sodium and water causing dehydration and hypotension, while glucocorticoid deficiency leads to weight loss, muscle weakness, hypoglycemia and eventual collapse.

Sheehan's syndrome is an eponymous name for post-partum necrosis of the pituitary gland. In pregnancy the anterior pituitary enlarges which compromises its blood supply from the low pressure portal veins. Any sudden cause of hypotension e.g. haemorrhage causing shock, further compromises the anterior pituitary and results in loss of function. Early symptoms include failure of lactation and amenorrhoea (lack of LH), or alternatively women experience gradual onset of the symptoms of secondary adrenal insufficiency.

### **Zona reticulosa**

Tumours can arise in this layer but it would seem only in women and even these are very rare. Signs and symptoms in women:

- hirsutism
- acne
- oligomenorrhea
- virilisation

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## ANSWERS TO QUESTIONS:

1.TTFTF 2.TFTFT 3.TTFTT 4.FFTTT 5.FTTFT

Q1.

- a. T
- b. T
- c. F The cortex produces aldosterone, cortisol and androgens.
- d. T
- e. F The zona reticularis produces androgens.

Q2.

- a. T
- b. F Norepinephrine is the precursor epinephrine.
- c. T
- d. F Cortisol stimulates gluconeogenesis.
- e. T

Q3.

- a. T
- b. T
- c. F Pheochromocytoma causes episodes of hypertension.
- d. T
- e. T

Q4.

- a. F Cushing's disease is caused by a pituitary adenoma. Cushing's syndrome may be caused by an adrenal tumour.
- b. F Causes weight gain.
- c. T
- d. T
- e. T

Q5.

- a. F Addison's disease is due to failure of the adrenal cortex.
- b. T
- c. T
- d. F There is a rise in ACTH due to failure to suppress the pituitary gland.
- e. T