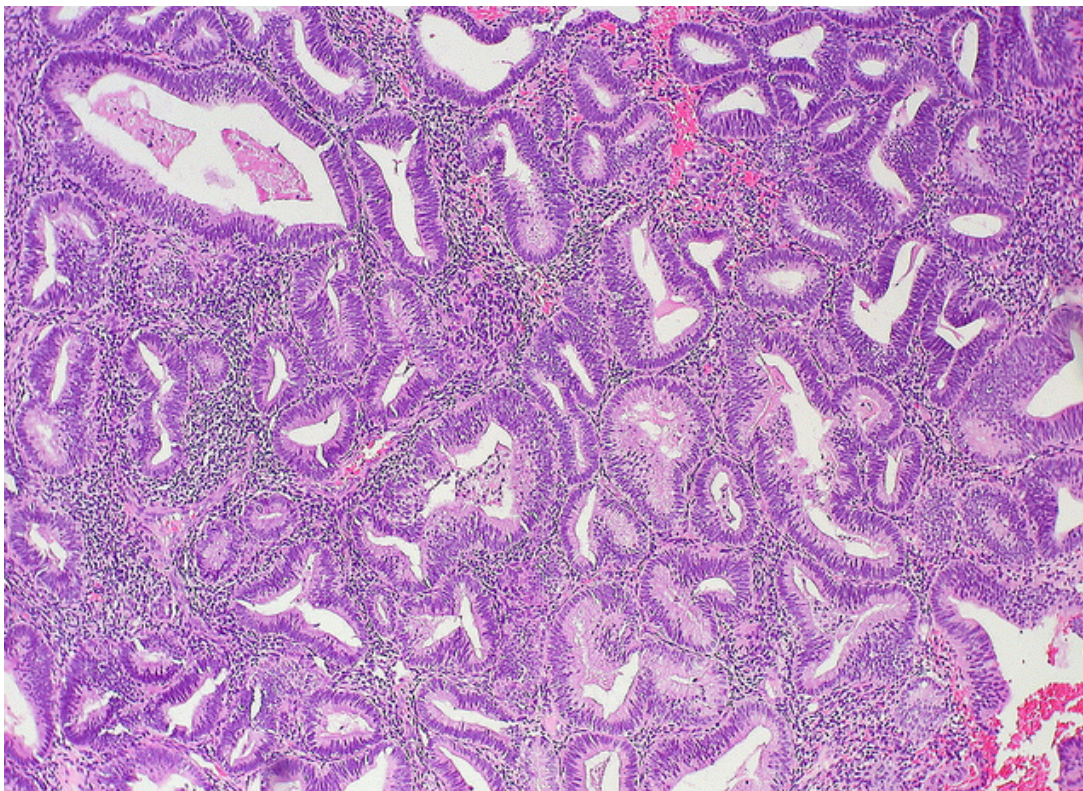


Adrenal Gland: Physiology, Pathology, and Pharmacology (Mineralocorticoids & Glucocorticoids)

[See online here](#)

Suprarenal glands are located on the superior pole of each [kidney](#). Each gland has two distinct developmental origins that divide it into two regions. The catecholamine secreting medulla is derived from the neural crest and is made of chromaffin cells. The cortex is derived from the mesoderm and it consists of three layers: the mineralocorticoid secreting zona glomerulosa, cortisol secreting zona fasciculata and the zona reticularis that secretes androgens. There are many common pathologies that can present, e.g., adrenal hypoplasia, hyperplasia and adrenal tumors specific to each region.



Adrenal Gland

The adrenal gland is **located on the superior pole of the [kidney](#) and is covered by the Gerota fascia**. The blood supply comes from three branches: inferior phrenic artery, renal artery and aortic branches.

Venous drainage occurs through the inferior vena cava on the right side and into the left renal vein on the left side. There are two distinct developmental origins of the adrenal

gland that divide it into two regions: the cortex and the medulla.

The cortex is derived from the mesoderm and it consists of three layers: zona glomerulosa, zona fasciculata, and zona reticularis.

The medulla is derived from the neural crest and is made of chromaffin cells.

Physiology of the Adrenal Gland

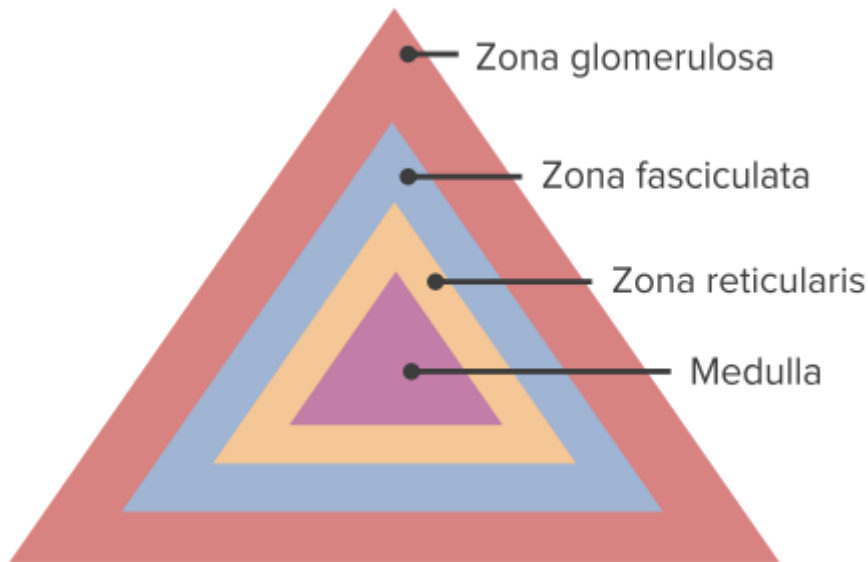


Image by Lecturio

Cortex

Zona glomerulosa

This is the outermost layer of the cortex. It **produces and secretes the mineralocorticoid aldosterone**. It is regulated by the renin-angiotensin system (RAAS).

Aldosterone acts on the [kidneys'](#) renal collecting ducts to promote sodium reabsorption and potassium excretion. Absorption of water is followed by sodium which will lead to an increase in extracellular fluid volume.

A loss of aldosterone would result in excretion of sodium, followed by water, leading to [dehydration](#), and due to its effects on potassium, it can lead to hyperkalemia and result in cardiac toxicity. **Excess aldosterone can lead to hypokalemia** and result in extreme fatigue and muscle weakness. Hydrogen can also be excreted and result in metabolic alkalosis.

As a component of the RAAS system, angiotensin II induces the release of aldosterone to increase fluid retention and ultimately [blood pressure](#).

Zona Glomerulosa cells also respond directly to high and low levels of sodium and potassium in the extracellular fluid to either stimulate aldosterone release in hyperkalemic states or to inhibit aldosterone release in hypernatremia.

Adrenocorticotropic hormone (ACTH) from the anterior pituitary stimulates aldosterone release.

Zona fasciculata

This is the middle layer of the cortex. It produces and secretes the glucocorticoid cortisol. It is **regulated by ACTH from the anterior pituitary**. For cortisol release, it is important to know that ACTH is regulated by a corticotropin-releasing hormone from the **hypothalamus**. There is a circadian component to cortisol regulation with the highest levels being in the morning and lowest being in the evening. Stress and other factors can influence how cortisol is regulated throughout the day.

Note: Cortisol acts to stimulate the **liver** to use proteins and free fatty acids for gluconeogenesis. This process increases liver glycogen levels and increases serum glucose.

Anti-inflammatory effects come from the prevention of lysosomal protein release through stabilization of membranes, decrease in capillary permeability and a decrease in white blood cell chemotaxis. Often time **with exogenous glucocorticoids you can see an increase in white cell count** because of this.

Thus, cortisol plays an important role in the increase in glycogen store in the liver, reduction in protein stores, increase in inflammatory reactions and reduction in immunity in an adverse manner.

Zona reticularis

The innermost layer of the cortex produces and secretes both male and female sex hormones. The male sex hormones are Dehydroepiandrosterone (DHEA), DHEA sulfate, androstenedione, and 11-hydroxy-androstenedione. The female sex hormones are in much smaller quantities of **progesterone and estrogen**.

The effect of the sex hormones mostly comes from their conversion of androgen outside of the adrenal gland into testosterone. Their effect is seen during male gonadal development and in females during puberty. ACTH stimulates its release.

For the USMLE, it will be important to remember those sex hormones are produced in this layer of the adrenal cortex and to be aware of the specific names of the hormones.

USMLE pearl: You can remember the order of the cortex with the phrase “Salty, sweet, sexy” or “It gets sweeter the deeper you go”.

Medulla

The medulla is composed of one cell type, the chromaffin cells. The chromaffin cells are derived from the neural crest and migrate to the adrenal medulla. Chromaffin cells secrete catecholamines: epinephrine, norepinephrine, and dopamine. The medulla is responsible for the release of epinephrine (80 %) and norepinephrine (20) with a very little secretion of dopamine into the blood under the influence of acetylcholine.

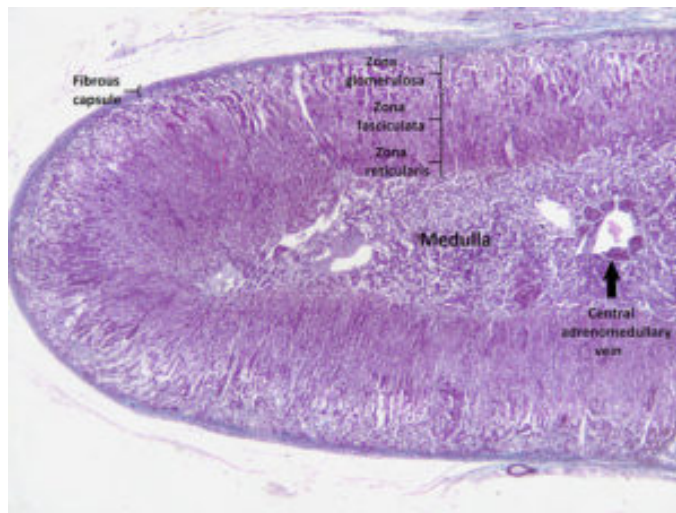


Image: "Adrenal cortex labeled" by Jpogi. License: [CC BY-SA 1.0](https://creativecommons.org/licenses/by-sa/1.0/)

The sympathetic nervous system stimulates the secretion of the catecholamines through acetylcholine release via preganglionic fibers originating in the thoracic spinal cord, from vertebrae T5-T11. Because it is innervated by preganglionic nerve fibers, the adrenal medulla can be considered as a specialized sympathetic ganglion. The **release of catecholamines leads to increased cardiac output and increased vascular resistance.**

Pathology of the Adrenal Gland

Hyperplasia

Hyperplasia **manifests itself through congenital adrenal hyperplasia**, which is due to an autosomal recessive disorder most commonly in the enzyme 21-hydroxylase. It is an enzyme necessary for cortisol production, which leads to ACTH oversecretion. Female patients will present at birth with [ambiguous genitalia](#).

Hypoplasia

Hypoplasia **manifests itself through a deficiency in ACTH**. It is commonly diagnosed in later childhood when the patient will present with [dehydration](#), hyponatremia, hyperkalemia, and hypotension.

The cortex has distinct pathology and expression depending upon each layer.

Zona glomerulosa

The zona glomerulosa can present with primary pathologies such as idiopathic adrenal nodular hyperplasia, adrenocortical carcinoma, and adenoma. Secondly, it can present with renal artery stenosis and renin tumors.

Zona fasciculata

The zona fasciculata can present with [Cushing syndrome](#). Cushing syndrome is caused by excess exogenous steroid or glucocorticoid secreting tumors. It is a **very common USMLE question topic**, and you should be very familiar with the material. Excess glucocorticoid production leads to the classic signs and symptoms of the moon-like facies,

acne, obesity, [hypertension](#), easy bruising, abdominal striae, and [osteoporosis](#). It is important to remember that there is also Cushing's disease, which is different from Cushing's syndrome. Cushing's disease is usually caused by a pituitary adenoma.

Zona reticularis

The zona reticularis can present with ambiguous genitalia in females and **can present in older children with pseudo precocious puberty and increased bone age**. These signs are most commonly seen in congenital adrenal hyperplasia and adrenal adenomas and carcinomas.

Pheochromocytoma

The most common pathology in the medulla is pheochromocytoma. The tumors will secrete catecholamines resulting in **symptoms of hypertension, headache, hyperhidrosis, palpitations, and pallor**. There are several genetic conditions that can predispose to pheochromocytoma: Von Hippel-Lindau (autosomal dominant defect in repair gene on Chr. 3) and MEN2A and 2B.

Investigative tests are to check urine for vanillylmandelic acid (VMA) from the breakdown of epinephrine and norepinephrine. **Treatment with α -blockers and β -blockers is for symptom relief** and a safe anesthetic induction, followed by surgical resection of the tumor.

The condition follows the '10 % rule', where 10% will be malignant, 10 % will be bilateral, 10 % outside the adrenal gland, 10 % calcify, and 10 % pediatrics.

In pediatric patients, [neuroblastoma](#) is the third most common pediatric cancer ([ALL](#) being the first). **Neuroblastoma accounts for 15 % of all pediatric cancer deaths**. It also originates from the neural crest and can be found in the adrenal medulla and sympathetic chain.

Exogenous Agents

Zona glomerulosa

The zona glomerulosa secretes aldosterone. When there is a loss of aldosterone, as seen in adrenal hypoplasia, the **mineralocorticoid fludrocortisone can be used to replace the aldosterone effects**. This treatment is often combined with salt tablets or free restriction of salt in the patient's diet.

Zona fasciculata

The zona fasciculata secretes glucocorticoids. They can be used in many different clinical settings, for instance, to treat [asthma](#) and decrease systemic inflammation. Direct replacement as seen in adrenal hypoplasia can be treated with long-term dexamethasone replacement.

Zona reticularis

The zona reticularis produces androgens that are converted in the periphery to testosterone. Exogenous testosterone can be used as a replacement.

Epinephrine

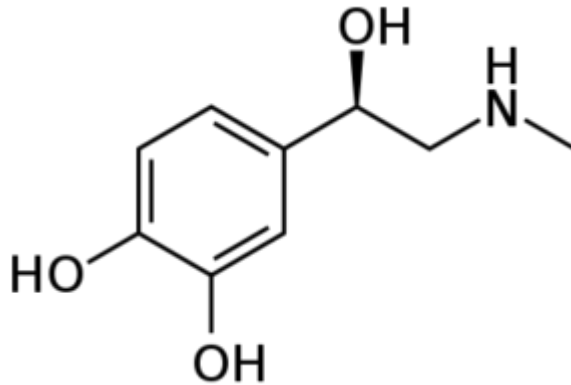


Image: "Epinephrine structure" by Acdx. License: [CC BY-SA 3.0](#)

In the medulla, the catecholamines epinephrine, norepinephrine and dopamine are released. It is secreted in response to stress, also known as adrenaline. Epinephrine acts to increase cardiac output through β_1 adrenergic receptors in the heart increasing cardiac output. It also acts to increase vasoconstriction through the α -adrenergic receptors. It can be used to treat [anaphylaxis](#), cardiac arrest, glaucoma, and hypotension.

Norepinephrine

Norepinephrine acts on both $\alpha_{1,2}$ and β_1 adrenergic receptors, and it has a much greater effect on the α receptors for vasoconstriction. It is also released in the medulla in response to stress, also referred to as stress hormone. It is used to treat shock and hypotension.

Dopamine

Dopamine is **often presented as a neurotransmitter** but is commonly used in the acute setting. It acts on both α and β receptors, it has a greater effect on cardiac function. It can be used to treat shock and [heart failure](#).

Mineralocorticoids

Aldosterone agonists

- Part of the RAAS
- Very strong salt-retaining activity

Fludrocortisone (Florinef)

→ structurally similar to cortisol

- Moderate glucocorticoid activity
- Strong mineralocorticoid activity
 - Cerebral salt wasting syndrome
 - [Addison's disease](#)
 - POTS (Paroxysmal Orthostatic Tachycardia Syndrome)
 - Geriatric orthostatic hypotensive syncope

Spirolactone, eplerenone

- Discusses in combination with [diuretics](#)
- Also used to treat [hirsutism](#) (mild anti-androgen activity)

Glucocorticoid

Glucocorticoid enters the cell as a free molecule.

- Binds to an intracellular receptor or other proteins
- Enters nucleus
- Binds to the glucocorticoid response element (GRE) which is a portion of DNA
- GRE regulates gene expression and transcription.

Side Effects

- **Metabolic:** gluconeogenesis, lipolysis, reduced subdermal fat
- **Morphologic:** lipid deposit in certain spots (Face, neck, shoulder)
- **Catabolic:** protein catabolism, tissue wasting, osteoporotic effects
- **Immunosuppressive:** cell-mediated immunity (i.e. lymphocyte dependent)
- **Renal:** cortisol is normally required for water excretion
- **Anti-inflammatory:** dramatic suppression of multiple markers
- **Neuropsychiatric:** excess cortisol causes giddiness, euphoria

Prednisone, active metabolite prednisolone

- Longer half-life, better membrane penetration
- Used in acute inflammation, and steroid replacement

Dexamethasone

- Longer half-life, better membrane penetration
- Potent; often used in cancer therapies

Triamcinolone

Beclomethasone, budesonide

- Readily penetrate the airway mucosa; used in inhalers

Synthesis inhibitors

Ketoconazole	Metyrapone	Aminoglutethimide
Antifungal drug	Inhibits synthesis of cortisol but not cortisol producers	Blocks conversion of cholesterol to pregnenolone
Used in adrenal adenoma, breast cancer, prostate cancer	Used in diagnostic tests of adrenal function	Used in steroid-producing adrenocortical cancers
Used in hirsutism		

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Notes