# *Adrenals and Stress Hormones*

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This lecture covers the role of the adrenal glands. The major topics covered will be the regulation of salt balance by aldosterone and stress responses mediated by adrenal gland secretions. This lecture covers the following pages in the textbook: 169, 321,326, 344-349, 394-5, 514-5 and 583[1].

[1] E Widmaier, H. Raff, and K. Strang. *Vander's Human Physiology: The Mechanisms of Body Function*. McGraw-Hill Science/Engineering/Math, 13th edition, 2013. ISBN 0073378305

## *Contents*

## *Learning Objectives*

For this lecture, the learning objectives are:

- Name three zones in the adrenal cortex and major regulator(s) of each zone.
- Name three steroidogenesis pathways and their major products.
- Explain briefly the physiological mechanism of adrenogenital syndrome.
- Describe the physiological actions and roles of aldosterone.
- Explain briefly the renin-angiotensin system.
- Describe the negative feedback regulation of aldosterone and its relationship to blood volume/blood pressure homeostasis.
- Describe hepatic and extrahepatic metabolic actions of glucocorticoids. Discuss their relationship.
- State the major findings caused by adrenal hypersecretion of mineralocorticoids.
- State the major findings caused by adrenal hypersecretion of glucocorticoids.
- Name the major hormones secreted from the adrenal medulla. Discuss the differences of epinephrine (epi) and norepinephrine (NE) in cardiovascular actions (physiological levels).
- List the major metabolic actions of catecholamines.
- Contrast the thresholds for actions vs. plasma levels of epi and NE under common conditions, like exercise, and in the disease pheochromocytoma

## *Anatomy of the Adrenal Gland*

The adrenal gland is located above the kidney and releases hormones in response to either nervous or hormonal stimulation. The central part of the adrenal gland, known as the adrenal medulla releases epinephrine and norepinephrine which are biogenic amines. The three regions of the adrenal medulla[2] release steroid hormones including aldosterone[3], cortisol[4], and the androgens (see Figure 1).

[2] zona glomerulosa, zona fasciculata and zona reticularis
[3] a mineralcorticoid
[4] a glucocorticoid

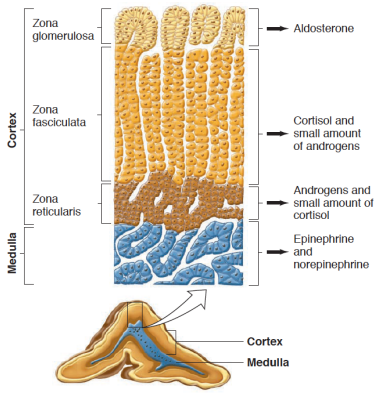


Figure 1: The anatomy of the adrenal gland.

[5] ACTH for cortisol; Angiotensin II for aldosterone

## *Steroid Hormones Secreted from The Adrenal Gland*

Steroid hormones are synthesized from cholesterol via enzymes which are regulated by PKA signaling. In response to the synthetic signal[5], the GPCR's are activated resulting in cAMP/PKA or $IP_3$ signaling cascades. Since steroid hormones are membrane soluble they can be released from the cell. They move through the serum bound to proteins called globulins which keep them soluble in the blood stream. Both aldosterone and cortisol signal via nuclear receptor signaling mechanisms in their target cells.

### *Aldosterone*

Aldosterone, which is a mineralcorticoid is primarily responsible for sensing and modulating salt balance at the kidney. It is produced in the adrenal cortex in a region called the zona glomerulosa. The main site of action of aldosterone is the cortical collecting ducts and the distal convoluted tubule, where it functions to stimulate sodium re-absoroption.

The mineralcorticoid receptor binds to aldosterone, which then promotes the transcription of three important genes involved in salt reuptake:

*Sodium/potassium pumps.* These pumps exchange sodium for potassium, to move sodium out of the kidney and back into the blood.

*ENac* This is a sodium transporter that helps get sodium from the tubule into the cells of the collecting duct.

*SGK1* Is a protein kinase that activates several transporters by post-translational modification.

Together these genes when activated by aldosterone enhance the movement of sodium ions out of the kidney and back into the blood stream. In the absence of aldosterone, the human body would secrete about 35g of sodium chloride per day. When aldosterone levels are

high (due to reduced sodium concentration), nearly all sodium is reabsorbed. This complex system requires integration of information about blood volume, blood pressure and sympathetic activity. This integrated endocrine circuite is known as the renin/angiotensin system

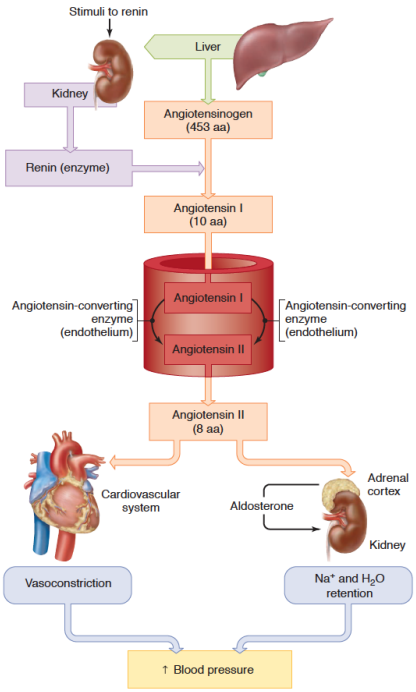


Figure 2: The renin/angiotensin system.

The Reinin-Angiotensin system. Angiotensin II[6] is generated by the liver as a precursor molecule called angiotensinogen. This molecule is processed in two stages to generate angiotensin II. The first, and most important regulatory step is mediated by a secreted enzyme known as renin. Renin is secreted from specialized pericytes near the kidney glomerulus known as juxtaglomerular cells[7]. When JG cells sense decreased stretch (decreased blood pressure), decreased glomerular flow or have elevated sympathetic nervous activity, Renin is released. Renin converts angiotensinogen to angiotensin I, which in turn is converted to angiotensin II by angiotensin converting enzyme. In this way, signaling to JG cells can cause increased angiotensin. Angiotensin then causes increased vasoconstriction[8] and increased salt reuptake. This pathway is illustrated in Figure 2.

[6] the active form

[7] JG cells, see Tigyi lectures for more information

[8] see lectures from O'Connell, Mancarella and Adebiyi

### *Cortisol*

Cortisol is synthesized and released from the zona fasciculata in response to stimulation by ACTH. As described previously in the

lecture on the anterior pituitary, ACTH is released from the corticotrophic cells of the pituitary in response to the hypothalamic hormone CRH. Cortisol is elevated under times of psychological stress and is also under the control of a circadian cycle[9]. Cortisol levels are normally highest in the morning, reaching a peak shortly before waking up and decline during the day.

[9] biological process that displays an endogenous, entrainable oscillation of about 24 hours. For more information see `http://en.wikipedia.org/wiki/Circadian_rhythm`

NIGHT SHIFT WORKERS, SUCH AS THOSE AS THE FEDEX FACILITY OFTEN HAVE ALTERED CIRCADIAN RHYTHMS AND ELEVATED CORTISOL LEVELS. This predisposes people who have abnormal circadian rhythms to have higher risk of diabetes, cardiovascular disease and sleep disturbances[10].

[10] Frank A J L Scheer, Michael F Hilton, Christos S Mantzoros, and Steven A Shea. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proceedings of the National Academy of Sciences of the United States of America*, 106(11):4453–4458, 2009. ISSN 0027-8424. DOI: 10.1073/pnas.0808180106; and An Pan, Eva S. Schernhammer, Qi Sun, and Frank B. Hu. Rotating night shift work and risk of type 2 diabetes: Two prospective cohort studies in women. *PLoS Medicine*, 8(12), 2011. ISSN 15491277. DOI: 10.1371/journal.pmed.1001141

THE PRIMARY ROLE OF CORTISOL IS TO MAINTAIN BLOOD GLUCOSE IN TIMES OF CHRONIC STRESS. Since most tissues, including the brain require glucose but do not store large amounts of glycogen and lipids they require a stable supply of glucose from the periphery. Glucose can be released from liver glycogen stores, or produced from precursor molecules[11] in the liver via a process known as gluconeogenesis. Cortisol, through its nuclear hormone receptor the glucocorticoid receptor, activates the transcription of several important gluconeogenic genes in the liver including PEPCK and Pyruvate carboxylase. To ensure that sufficient precursors are available for hepatic gluconeogenesis, cortisol also activates the breakdown of muscle protein[12] and adipose triglycerides[13]. Finally, cortisol induces resistance to insulin in muscle, adipose and liver tissues. Normally, insulin functions to pull glucose out of the blood and into muscle and adipose tissue, but cortisol prevents this, in order to maintain glucose levels in the blood.

[11] amino acids and fatty acids

[12] this is known as proteolysis

[13] this is known as lipolysis

A SECOND MAJOR ROLE OF CORTISOL IS TO SUPPRESS IMMUNE FUNCTION. Immune responses are energetically quite costly, so in line with directing nutrients to the brain during stress, immune function is decreased.

LOCAL CONCENTRATIONS OF CORTISOL are regulated by enzymatic inactivation by an enzyme known as 11$\beta$-hydroxysteroid dehydrogenase 2. This enzyme serves two important roles. One is to allow for local (tissue-specific) negative feedback of the cortisol signal. The other is to prevent tissues that should respond to aldosterone from accidentally responding to elevated levels of the chemically similar cortisol. By elevating 11$\beta$-hydroxysteroid dehydrogenase 2 activity, cortisol is converted to cortisone which has less affinity for the glucocorticoid receptor.

Another negative feedback mechanism for cortisol is that elevated cortisol levels suppress the release of both CRH (from the hypothalamus) and ACTH (from the anterior pituitary). This integrated circuit is known as the HPA[14] axis. Cortisol functions at several steps in the immune response, including suppressing both the innate and adaptive immune system. This is one of the reasons that prednisone[15] is used as in autoimmune diseases such as asthma, arthritis and allergic disorders.

[14] hypothalamus-pituitary-adrenal

[15] a synthetic glucocorticoid

### *Epinephrine and Norepinephrine*

In contrast to the steroid hormones described above, the adrenal medulla secretes epinephrine and norepinephrine, two water soluble biogenic amines.

### *Pathophysiology Related to Adrenal Hormones*

Cushings's disease is the result of elevated cortisol levels, either due to a pituitary tumor which constitutively secretes ACTH, or an adrenal tumor which secretes too much Cortisol.

Congenital Adrenal Hypertrophy[16] results from mutations in the biosynthesis genes involved in the production of steroid hormones.

[16] also known as adrenogenital syndrome

Addison's disease is due to immune destruction of the adrenal gland, functionally also preventing steroid hormone production.

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### *References*

An Pan, Eva S. Schernhammer, Qi Sun, and Frank B. Hu. Rotating night shift work and risk of type 2 diabetes: Two prospective cohort studies in women. *PLoS Medicine*, 8(12), 2011. ISSN 15491277. doi: 10.1371/journal.pmed.1001141.

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