

## The Adrenal Cortex and Medulla

These notes are supplementary to the packet; like Pierre said, we can all read, so I'm filling in the gaps. Notes are taken from Costanzo's Physiology—NOT the BRS, but the Starz/Saunders series. Hope you find it helpful!

### Introduction (pg.1 of packet)

“Adrenal” means near kidney, so the adrenal glands are located in the retroperitoneal cavity above each kidney. The adrenal gland is composed of two separate glands- the adrenal cortex and the adrenal medulla. The adrenal is active in fetal life, and then becomes quiescent.

The adrenal gland is essential for life, especially in situations such as maintaining homeostasis and responding to stressful conditions. The four areas that Dr. K mentioned were:

1. salt and water balance
2. maintenance of blood pressure
3. carbohydrate balance
4. immune system

	Cortex	Medulla
Origin	Mesoderm Differentiates by gest. week 8, produces fetal adrenal steroids (i.e. DHEA-S*) throughout uterine life; fetal adrenal cortex involutes after birth; replaced by the 3 layers of the adrenal cortex	Neuroectoderm
Secretions	adrenocortical steroid hormones glomerulosa- mineralocorticoids fasciculata- glucocorticoids reticularis- androgens	Epinephrine, norepinephrine
Location	Outer zone (80% of tissue)	Inner zone (20% of tissue)

\* DHEA-S is a steroid hormone that is produced by the fetal adrenal zone. Receptors for DHEA-S are located on fetal placental cell. Fetal placental cells use DHEA-S to make estrogen because fetal placental cells do not have cortisol responsive enzymes that are needed to make estrogen from progesterone.

### Structure of adrenocortical steroids

All of the steroids of the cortex are chemical modifications of a basic steroid nucleus that consists of a carbon skeleton with carbons labeled 1-21 and four rings (A,B,C,D). The bottom of pg.1 designates which carbons for which steroids.

In Table 20-1, cortisol and corticosterone fall into the glucocorticoid group, while aldosterone, deoxycorticosterone, and dehydroepiandrosterone fall into the mineralocorticoid group. Table 20-2 describes activity; note that dexamethasone has no mineralocorticoid activity.

### Synthesis of glucocorticoids

Each layer of the cortex synthesizes and secretes predominantly one type of steroid: glucocorticoid, mineralocorticoid, or androgen; the specialization is based on the presence or

absence of the enzymes that catalyze modifications of the steroid nucleus. The zona reticularis makes androgenic steroids because it has 17,20-lyase; zona glomerulosa makes aldosterone because it has aldosterone synthase. Cholesterol is provided to the cortex through circulation, in addition to small amounts that are made within the adrenal cortical cells. Cholesterol circulates bound to low-density lipoproteins; lipoprotein receptors are in the membranes of adrenocortical cells; after binding, the complex is endocytosed inside, where cholesterol is esterified and stored in cytoplasmic vesicles until it is used to make steroids.

In order to initiate the conversion of cholesterol to active steroid hormones, cytochrome P-450 is required, along with oxygen and NADPH (hydrogen donor). The first step in each pathway (in all three layers) is the conversion of cholesterol to pregnenolone, catalyzed by cholesterol desmolase. Cholesterol desmolase is stimulated by ACTH.

Metyrapone inhibits glucocorticoid synthesis by blocking 11-hydroxylase, which is the last step in cortisol synthesis. Ketoconazole inhibits several steps in the pathway, including the first step.

### Synthesis of androgens

The zona reticularis produces DHEA and androstenedione; these have weak androgenic activity, but they are converted to testosterone in the testes. The testes produce their own testosterone from cholesterol, but the adrenal cortex plays a more significant role in producing androgens for the female. Before menopause, half of estrogen comes from the ovary, the other half from the adrenal. After menopause, all estrogen is from the adrenal.

### Synthesis of mineralocorticoids

The major product from this layer is aldosterone. It follows the same steps to make corticosterone, and then aldosterone synthase (has 18-hydroxylase activity) converts corticosterone to aldosterone. Note the hydroxylation reaction to get aldehyde form of aldosterone to hemiacetal form.

### Transport and metabolism

CBG (cortisol binding globulin) is made in the liver

Cortisol is stabilized by glucuronide and/or sulfation; then water soluble for excretion.

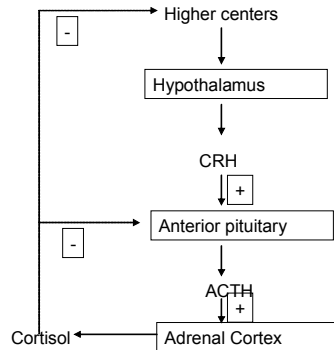
### Activation and regulation

Without ACTH, biosynthesis of all the steroids from the cortex ceases.

Layer	Zona fasciculata	Zona reticularis	Zona glomerulosa
Regulation system	Hypothalamic-pituitary axis	Hypothalamic-pituitary axis	ACTH + renin-angiotensin-aldosterone system
Regulatory components	Corticotropin-releasing hormone (CRH), ACTH	CRH, ACTH	Low blood pressure

## Glucocorticoid regulation and secretion

Here's a flow chart for regulation of cortisol secretion (same thing on pg. 5, but I added the positive and negative feedbacks):



CRH travels to the pituitary via the hypothalamic-hypophysial portal blood. It then acts on the corticotrophs by adenylyl cyclase/cAMP pathway to cause secretion of ACTH into the bloodstream. ACTH has several effects on the adrenal cortex. Immediately, it stimulates transfer of stored cholesterol to the mitochondria, stimulate binding of cholesterol to cytochrome P450, and activate cholesterol desmolase (bottom line: activate desmolase to generate glucocorticoid hormones).

Regulation of cortisol is pulsatile in nature and has a diurnal pattern. The lowest secretions occur during the evening and just after falling asleep; the highest occur before awakening (one half of total daily cortisol secretion). At awakening, there is a slight delay in the rise of cortisol compared to ACTH—it's stressful to wake up! The diurnal pattern can be abolished by coma, blindness, or constant exposure to light or dark.

## Actions of glucocorticoids

Adrenocortical steroids have diverse actions. The actions first require transcription of DNA, synthesis of specific mRNAs, and induction of new protein synthesis. The new proteins confer specificity to the steroid hormone actions in target tissues.

Below are some background information of some of the effects of glucocorticoids, the rest (mostly on pg. 7) are well explained in the packet:

- Glucocorticoids are essential for life; they are essential for gluconeogenesis, vascular responsiveness to catecholamines, suppression of inflammatory and immune responses, and for modulation of CNS function. Cortisol promotes gluconeogenesis and storage of glycogen, leading to catabolic and diabetogenic effects. It affects metabolism to increase glucose synthesis, such as by increasing protein catabolism in muscle, decreasing new protein synthesis (amino acids are directed to liver for gluconeogenesis), increasing lipolysis. It also decreases glucose utilization by tissues and decreases the insulin sensitivity of adipose tissue.
- Glucocorticoids down regulate ACTH secretion due to the negative feedback loop.
- Cortisol is necessary for the maintenance of normal blood pressure; it up regulates adrenergic receptors, making it responsible for the vasoconstrictive response of arterioles to catecholamines.

- d. Glucocorticoid receptors are found in the limbic system of the brain. It decreased REM sleep, increases slow-wave sleep, and increases wake time. Without glucocorticoids, there is increased irritability, loss of concentration, increased sense of smell and taste.
- e. Cortisol increases GFR by causing vasodilation of afferent arterioles.
- f. Immune system is down (but anti inflammatory!); there is decrease in size, decrease in number of antibodies produced, immune system suppressed, so endogenous glucocorticoids are good for transplant surgery. Cortisol inhibits the synthesis of the precursor to prostaglandins and leukotrienes. It also inhibits the production of IL2 and the proliferation of T lymphocytes, and inhibits the release of histamine and serotonin from mast cells and platelets.

### Adrenal Androgen Regulation and Action

Androgen synthesis is also regulated by ACTH, but does not have feedback effects as does cortisol. In adrenogenital syndrome, there is increased synthesis of adrenal androgens. The high levels of DHEA and androstenedione lead to masculinization in females, early development of axillary and pubic hair, and suppression of gonadal function in both males and females.

### Regulation and actions of mineralocorticoids

ACTH is still essential for aldosterone secretion since it stimulates the cholesterol desmolase, but the primary regulation of aldosterone secretion is the change in ECF volume via the renin-angiotensin II-aldosterone system and through changes in the serum potassium levels. The mechanism for this system and the action of aldosterone is pretty thoroughly discussed on pgs 8 and 9; and we've had this a zillion times already, so I'll leave the details out. The basic outline is this: low blood pressure sensed JG cells leads to release of renin (from the JG cells) → renin cleaves angiotensinogen I to make angiotensin I → angiotensin I is converted to angiotensin II by ACE in the lung → angiotensin stimulates secretion of aldosterone by binding to receptors in the zona glomerulosa. Aldosterone induces reabsorption of sodium by the kidney, and wherever sodium goes, water follows, so blood pressure will increase under the influence of this system.

### Pathophysiology

Addison's Disease is primary adrenocortical insufficiency. It is commonly caused by autoimmune destruction (antibodies) of all zones of the adrenal cortex. There is decreased synthesis of all adrenocortical hormones. ACTH levels must be high, not low; the hypothalamus pituitary axis is normal, but the cortex is not responding.

Cushing's syndrome is the result of chronic excess of glucocorticoids. It can be caused by spontaneous overproduction of cortisol by the adrenal cortex or from the administration of pharmacological doses of exogenous glucocorticoids. Cushing's *disease* is separate; the excess glucocorticoids is caused by hypersecretion of ACTH from a pituitary adenoma. The plasma levels of ACTH could be used for diagnosing the difference between the two. Cushing's syndrome has a primary defect in the cortex, which is overproducing cortisol, but the pituitary is normal and ACTH levels are low. In Cushing's disease, the primary defect is in the anterior pituitary, which is overproducing ACTH; the ACTH levels are elevated. In this case, the patient may also get excess androgens that leads to virilization since androgen synthesis is also under ACTH regulation. Cushing's syndrome can be treated by drugs (i.e. metyrapone) that block steroid hormone synthesis. Cushing's disease should be treated by surgical removal of the ACTH secreting tumor.

Effects of Cushing's:

1. increase in protein catabolism
2. increase in depositions of glycogen
3. increase in lipolysis
4. effects on CNS
5. important anti-inflammatory effects

Conn's syndrome is primary hyperaldosteronism, which is caused by an aldosterone secreting tumor. It can also be secondary to excess renin production. Spironolactone is an aldosterone antagonist that could be used to treat the disease, followed by surgical removal of the aldosterone/renin secreting tumor.

### Overall Schematic

The diagram on pg. 12 shows steroid production in the adrenal. If there is a block in the flow so that the precursors build up, it will result in shunting towards other pathways. Oftentimes, it results in androgen production, which will lead to virilization. There is also no negative feedback, so even more precursors are being made.

Last note for adrenal cortex: The treatment for enzyme deficiency pathology includes cortisol/aldosterone analogs.

### Adrenal Medulla

The adrenal medulla is a specialized ganglion in the sympathetic division of the autonomic nervous system. The cell bodies are located in the thoracic spinal cord and the axons of the preganglionic neurons travel in the greater splanchnic nerve to the adrenal medulla, where they synapse on chromaffin cells to release ACh. Regulation is by the sympathetic nervous system (i.e. response to stress) and the action is to release epinephrine and norepinephrine into the general circulation. ACTH and cortisol can also have stimulatory effects. Normal sympathetic neuron terminals make norepinephrine; the cells in the adrenal medulla have enzymes that can methylate norepinephrine and convert it to epinephrine. VMA is a biologically inactive breakdown product of catecholamines; the presence of VMA in the urine indicates high metabolism of catecholamines.

Binding of alpha receptors will lead to increase in cGMP. Binding to beta receptors will lead to increase in cAMP. Binding of the catecholamines lead to many different effects; they're summarized in the tables on pg. 17. One aspect is fuel metabolism; generally, epinephrine increases glycogenolysis and lipolysis to create a rise in plasma glucose, free fatty acids, and ketoacids.

### Pathophysiology

Pheochromocytoma causes large amounts of catecholamines