

# CPY 605 ADVANCED ENDOCRINOLOGY

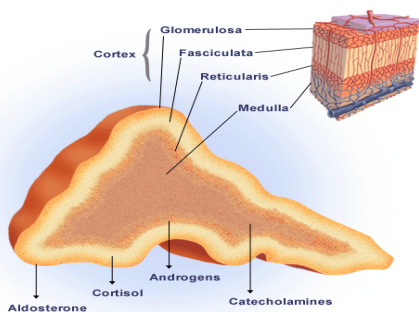
## THE ADRENAL CORTEX

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## INTRODUCTION

- Two adrenal glands lie on top of each kidney.
- Each gland between 6 and 8g in weight is composed of a cortex and medulla.
- The cortex makes steroid hormones and the medulla catecholamines
- The cortex is composed of 3 histologic zones
  - Zona glomerulosa
  - Zona fasciculata
  - Zona reticularis as seen below

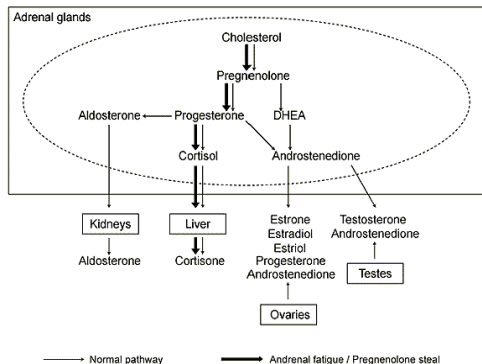
### Anatomy of the Adrenal Cortex



### Hormones secreted by the adrenal cortex

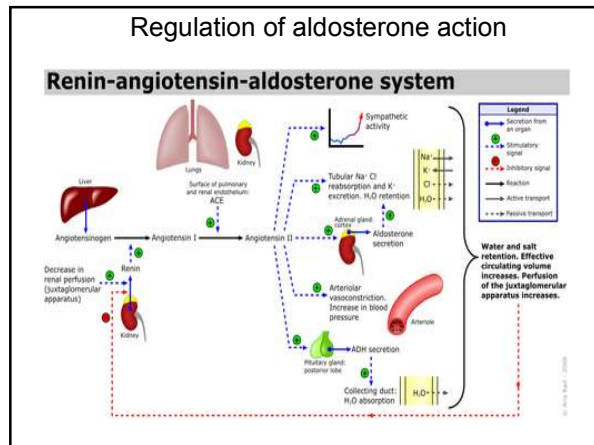
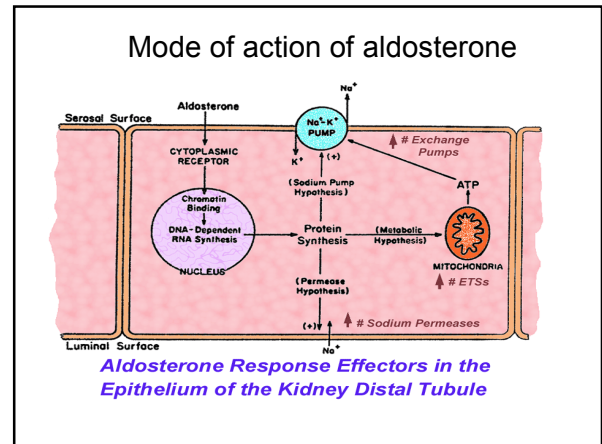
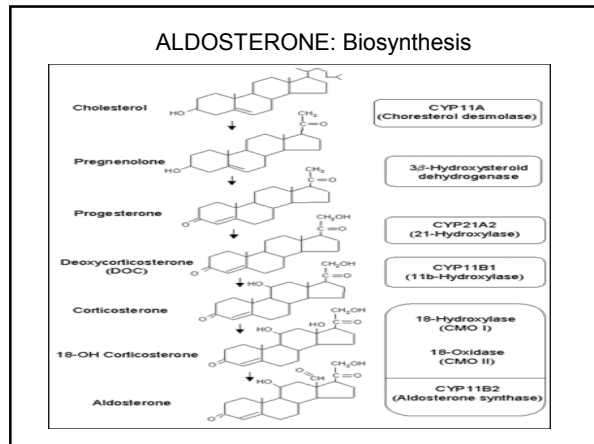
- **Aldosterone**: produced by the outermost zona glomerulosa. It is the primary mineralocorticoid in humans
- **Cortisol**: produced by the zona fasciculata. It is the primary glucocorticoid in humans
- **“Adrenal androgens”**: produced by the zona reticularis.
- Adrenal androgens are androgen and oestrogen precursors, the parent compound being **dehydroepiandrosterone**.

### Steroid Hormone Synthesis Pathways

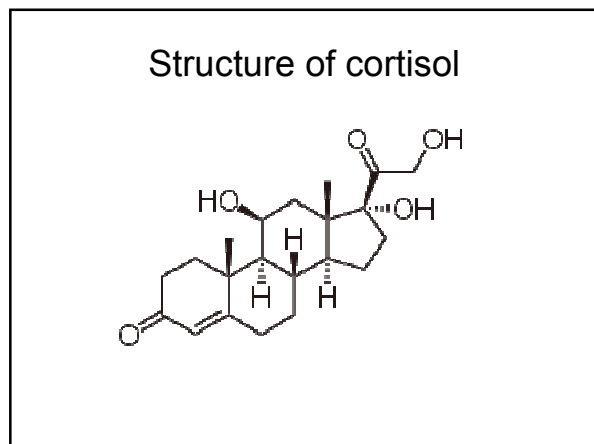


## ALDOSTERONE

- It is an essential hormone for life
- It acts on the distal tubule of the nephron where it causes reabsorption of sodium as a response to signals from the renin angiotensin system.
- It is thus very crucial in maintaining water and electrolyte balance.
- In it's absence this balance is distorted leading to a series of biochemical changes e/g alkalosis, acidosis with the end point being death.



- ### CORTISOL
- Cortisol**, also known as **hydrocortisone**, is a corticosteroid hormone or glucocorticoid produced by the zona fasciculata of the adrenal cortex
  - Chemical formula:  $C_{21}H_{30}O_5$
  - IUPAC name: (11 $\beta$ )-11,17,21-trihydroxypregn-4-ene-3,20-dione
  - It is also an essential hormone with receptors in virtually every cell in the body.



- ### PHYSIOLOGY OF CORTISOL
- The name "glucocorticoid" derives from early observations that these hormones were involved in glucose metabolism. In the fasted state, cortisol stimulates several processes that collectively serve to increase and maintain normal concentrations of glucose in blood.
  - The amount of cortisol hormone present in the blood undergoes diurnal variation, with the highest levels present in the early morning (approximately 8am), and the lowest levels present around 12-4am, or 3-5 hours after the onset of sleep.

## Physiology con't

- Metabolic effects:

**Stimulation of gluconeogenesis, particularly in the liver:** This pathway results in the synthesis of glucose from non-hexose substrates such as amino acids and glycerol from triglyceride breakdown, and is particularly important in carnivores and certain herbivores. Enhancing the expression of enzymes involved in gluconeogenesis is probably the best-known metabolic function of glucocorticoids.

**Mobilization of amino acids from extrahepatic tissues:** These serve as substrates for gluconeogenesis.

**Inhibition of glucose uptake in muscle and adipose tissue**

This is done by decreasing the translocation of glucose transporters to the cell membrane, specially GLUT4 : A mechanism to conserve glucose.

**Stimulation of fat breakdown in adipose tissue:**

The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis.

## PHYSIOLOGY CON'T

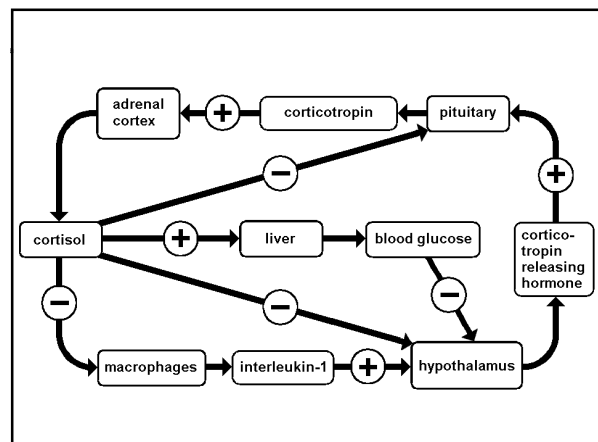
- In normal release, cortisol (like other [glucocorticoid](#) agents) has widespread actions which help restore homeostasis after stress
- It increases blood pressure by increasing the sensitivity of the vasculature to epinephrine and norepinephrine. In the absence of cortisol, widespread vasodilation occurs.
- Cortisol prevents proliferation of T-cells by rendering the interleukin-2 producer T-cells unresponsive to interleukin-1 (IL-1), and unable to produce the T-cell growth factor. It lowers bone formation thus favoring development of osteoporosis in the long term.

- Cortisol inhibits loss of sodium from small intestines of mammals. However, sodium depletion does not affect cortisol, so cortisol is not used to regulate serum sodium.
- Cortisol moves potassium out of cells in exchange for an equal number of sodium ions. This can cause a major problem with the hyperkalemia of metabolic shock from surgery.
- Cortisol reduces calcium absorption in the intestine.

- It cooperates with epinephrine (adrenaline) to create memories of short-term emotional events; this is the proposed mechanism for storage of flash bulb memories, and may originate as a means to remember what to avoid in the future. However, long-term exposure to cortisol results in damage to cells in the hippocampus. This damage results in impaired learning.

## Regulation of cortisol action

- The primary control of cortisol is the pituitary gland peptide, adrenocorticotropic hormone (ACTH).
- ACTH is in turn controlled by the hypothalamic peptide, corticotropin releasing hormone (CRH), which is under nervous control. CRH acts synergistically with arginine vasopressin, angiotensin II, and epinephrine.
- Activated macrophages also secrete interleukin-1 (IL-1), which acts synergistically with CRH and thus either increases or decreases ACTH.



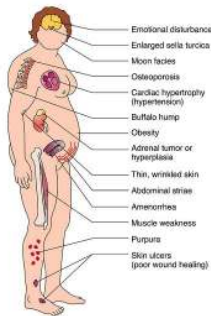
## Dehydroepiandrosterone

- 5-Dehydroepiandrosterone (5-DHEA) is an endogenous steroid that has been implicated in a broad range of biological effects in humans and other mammals. Together with its sulfate ester (DHEA-S), it is the most abundant steroid in humans.
- DHEA is produced by the zona reticularis, but also synthesized de novo in the brain.
- It acts on the androgen receptor both directly and through its metabolites, which include androstenediol and androstenedione, which can undergo further conversion to produce the androgen testosterone and the estrogens estrone and estradiol.
- DHEA can thus be understood as a prohormone for the sex steroids.

## DISORDERS OF THE ADRENAL CORTEX

- **Cushing's syndrome (excess cortisol)**
- ACTH Dependent causes (Values of ACTH > 10pg/dl)
  - ACTH secreting pituitary tumour
- ACTH independent causes (values < 10pg/dl)
  - Adrenal adenoma
  - Adrenal carcinoma
  - Micronodular adrenal disease
  - Excess glucocorticoid administration
  - The differentiation is based on the plasma ACTH concentration following administration of CRH

## Symptoms of Cushing's syndrome



## HYPERALDOSTERONISM (Excess mineralocorticoid)

- It can be renin – angiotensin independent or dependent
- The 2 forms can be differentiated on the basis of plasma renin activity
- If resting plasma renin activity is high then the excess is renin – angiotensin dependent
- If plasma renin activity is low and cannot be stimulated by 4 hours of upright posture then the excess is renin – angiotensin independent.
- Symptoms include arterial hypertension and dependent oedema, hypokalaemia and metabolic alkalosis.

## Common causes of renin - angiotensin independent mineralocorticoid excess

- Aldosterone secreting adenoma
- Adrenal cancer
- Congenital adrenal hyperplasia
- 11beta hydroxysteroid dehydrogenase deficiency (failure of conversion of cortisol to cortisone)

## Common causes of renin – angiotensin dependent mineralocorticoid excess

- Vomiting
- Congestive heart failure
- Hepatic cirrhosis
- Nephrotic syndrome
- Renin secreting tumours.

## ADDISON'S DISEASE

- Addison's disease (also chronic adrenal insufficiency, hypocortisolism, and hypocorticism) is a rare endocrine disorder wherein the adrenal glands produce insufficient steroid hormones (mainly glucocorticoids and sometimes mineralocorticoids).
- This can be caused by a disorder of the adrenal glands, autoimmune disorder, pituitary or hypothalamic dysfunction.

## Symptoms of Addison's disease

The most common symptoms are

- fatigue,
- dizziness,
- muscle weakness,
- weight loss,
- difficulty in standing up,
- anxiety,
- diarrhea,
- headache,
- Some have marked cravings for salt or salty foods due to the urinary losses of sodium.

Adrenal insufficiency is manifested in the skin primarily by hyperpigmentation.

### • The negative feedback loop for glucocorticoids.

Because primary hypocortisolism is manifested as a deficiency in glucocorticoid release from the adrenal cortex, increased ACTH will be released by the pituitary in order to trigger release of the absent glucocorticoid; it is because of this overstimulation of ACTH that bronzing of the skin occurs. In secondary or tertiary hypocortisolism, there is a deficiency of either CRH or ACTH release by the hypothalamus or pituitary gland, respectively. The former will manifest as no ACTH release while the latter will manifest as physiologic (normal) ACTH release; neither will cause an overproduction of ACTH.

## Mineralocorticoid deficiency

- This is a condition where circulating aldosterone levels are lower than normal
- The major clinical manifestations are
  - Hyponatraemia
  - Hyperkalaemia
  - Profound muscle weakness
  - Cardiac arrhythmias

The causes can be divided into renin dependent and renin independent based on plasma renin activity after 4 hours of upright posture.

### • Renin – angiotensin dependent (renin levels in the low range)

- Kidney disease (failure to secrete renin)
- Autonomic neuropathy (failure to stimulate the kidneys)

### • Renin – angiotensin independent (high renin levels)

- Autoimmune destruction of adrenal cortex.
- infection of the adrenal cortex
- Metastases

• Thank you