

Biochemistry of Addison's Disease

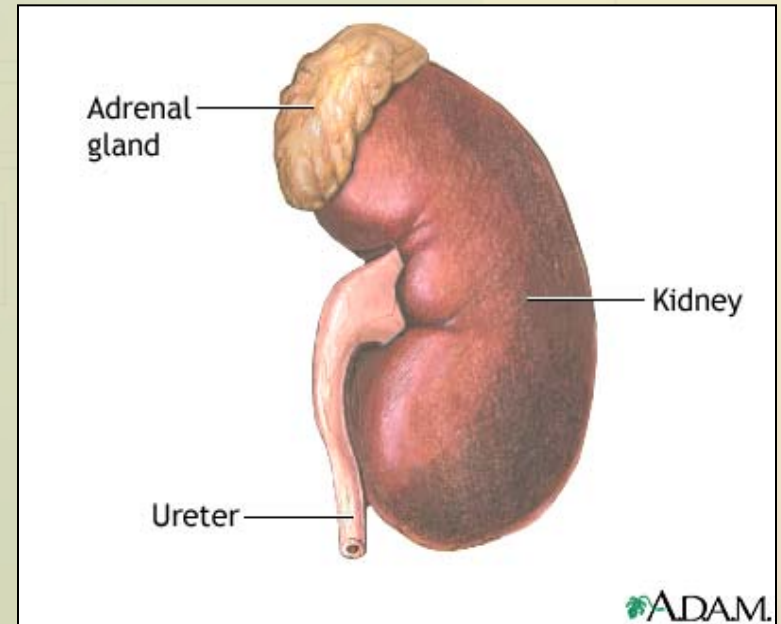
Endocrine Block

Objectives

- To identify different causes of primary adrenocortical hypofunction (Addison's disease)
- To identify secondary causes of adrenocortical hypofunction
- To understand the diagnostic algorithm for adrenocortical hypofunction
- To understand the interpretation of laboratory tests of adrenocortical hypofunction

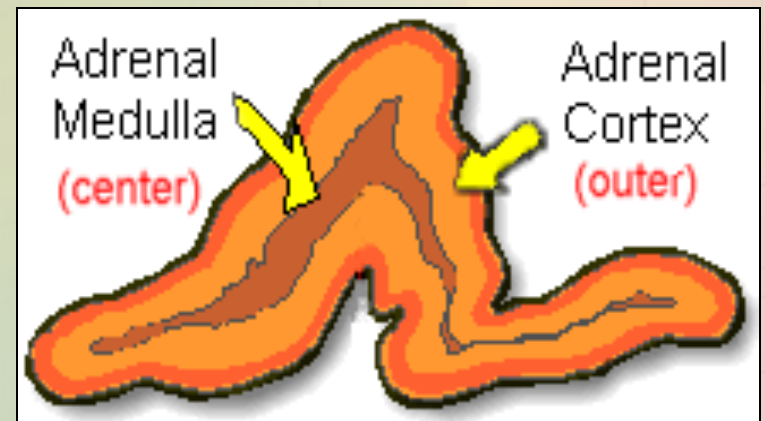
ANATOMICALLY:

- The adrenal gland is situated on the anterosuperior aspect of the kidney



HISTOLOGICALLY:

- The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla.



The adrenal cortex comprises three zones based on cell type and function:

➤ Zona Glomerulosa

The outermost zone → **aldosterone** (the principal mineralocorticoid).

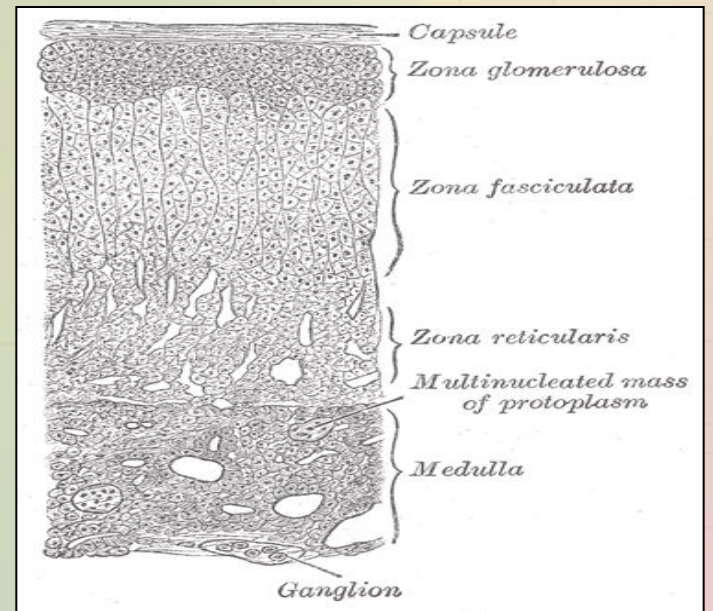
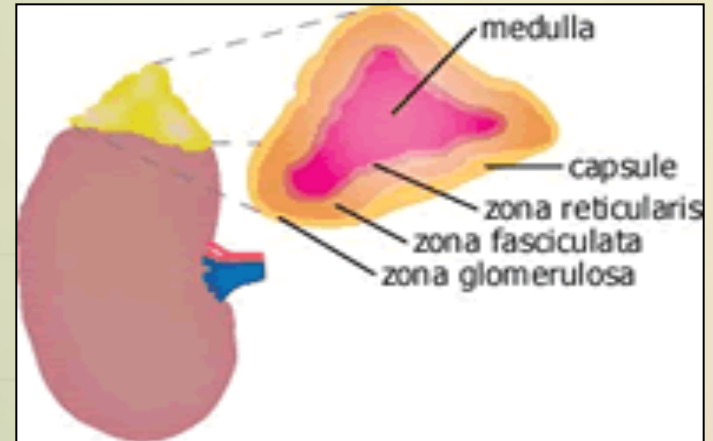
The deeper layers of the cortex:

➤ Zona Fasciculata

→ glucocorticoids – mainly **cortisol** (95%)

➤ Zona Reticularis

→ Sex hormones



Steroid Hormone Synthesis

Cholesterol (27C)



Pregnenolone (21C)



3- β -Hydroxysteroid dehydrogenase

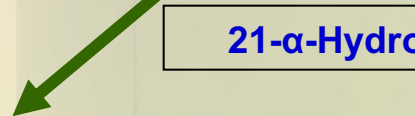
Progesterone (21C)



17- α -Hydroxylase

17- α -Hydroxyprogesterone (21C)

21- α -Hydroxylase



11-Deoxycorticosterone (21C)



Androstenedione (19C)

11-Deoxycortisol (21C)



11- β -Hydroxylase

Corticosterone



Aldosterone (21C)

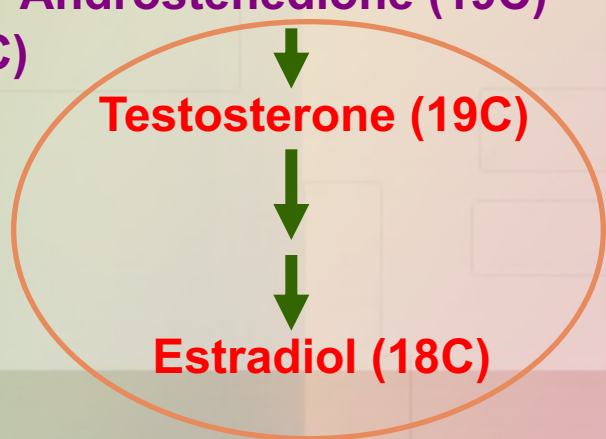
Cortisol (21C)

Testosterone (19C)



Estradiol (18C)

Peripheral tissues



Aldosterone Hormone

- The principal physiological function of aldosterone is to **conserve Na^+** , mainly by facilitating Na^+ reabsorption and reciprocal **K^+ or H^+ secretion** in the distal renal tubule.
- aldosterone is a **major regulator of water and electrolyte balance**, as well as **blood pressure**.

- **Aldosterone**, by acting on the distal convoluted tubule of kidney, leads to:
 - ↑↑ **potassium excretion**
 - ↑↑ **sodium and water reabsorption**
- **Renin-Angiotensin system** is the most important regulatory mechanism for aldosterone secretion

The renin - angiotensin system

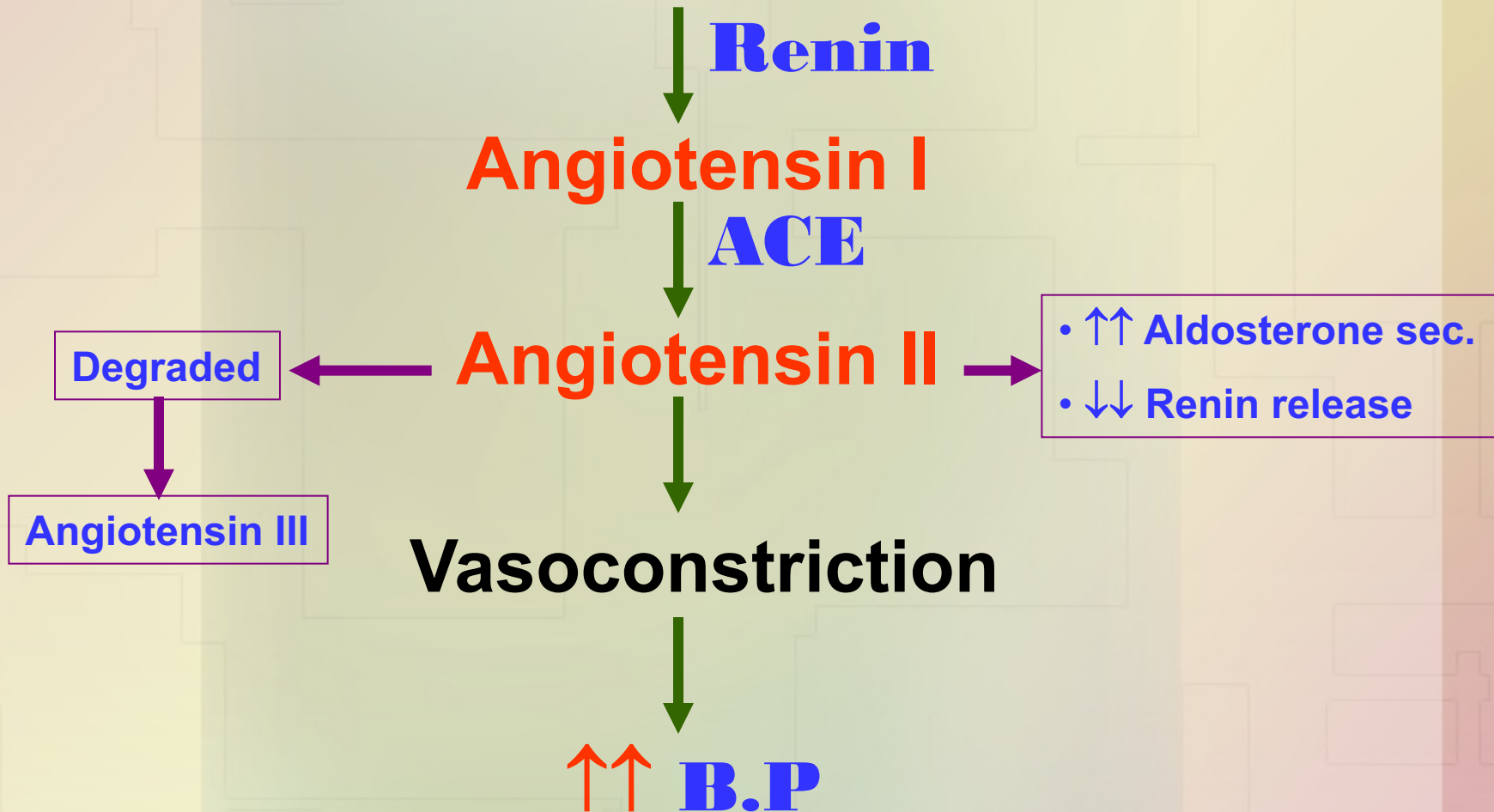
- It is the most important system controlling **aldosterone secretion**.
- It is involved in **B.P. regulation**.

Renin:

- a proteolytic enzyme produced by the **juxtaglomerular cells** of the afferent renal arteriole.
- **Sensitive to B.P. changes through baroreceptors**
- released into the circulation in response to :
 - a fall in circulating blood volume.
 - a fall in renal perfusion pressure.
 - loss of Na⁺.

Angiotensinogen

(α 2-Globulin made in the liver)



Causes of adrenocortical hypofunction (AC)

A. Primary AC hypofunction (destruction of adrenal gland, Addison's disease):

Autoimmune

Infection, e.g., tuberculosis

Infiltrative lesions, e.g., amyloidosis

B. Secondary AC hypofunction:

Pituitary tumors

Vascular lesions

Head trauma

Hypothalamic diseases

Iatrogenic (steroid therapy, surgery or radiotherapy)

Signs and symptoms of primary adrenal failure (Addison's disease)

The symptoms are precipitated by trauma, infection or surgery:

Lethargy, weakness, nausea & weight loss.

Hypotension especially on standing (postural)

Hyperpigmentation (buccal mucosa, skin creases, scars)

Deficiency of both glucocorticoids and mineralocorticoids

Hypoglycemia, ↓ Na⁺, ↑ K⁺ and raised urea

Life threatening and need urgent care.

Hyperpigmentation in Addison's disease

Hyperpigmentation occurs because melanocyte-stimulating hormone (MSH) and (ACTH) share the same precursor molecule, Pro-opiomelanocortin (POMC).

The anterior pituitary POMC is cleaved into ACTH, γ -MSH, and β -lipotropin.

The subunit ACTH undergoes further cleavage to produce α -MSH, the most important MSH for skin pigmentation.

In secondary adrenocortical insufficiency, skin darkening does not occur.

Investigation of Addison's disease (AD)

- The patient should be hospitalized
- **Basal measurement of:**
Serum urea, Na⁺, K⁺ & glucose
Serum cortisol and plasma ACTH
- Definitive diagnosis and confirmatory tests should be done later after crisis.

Investigation of Addison's disease (AD)

Cont'd

- Normal serum cortisol and UFC does not exclude AD.
- Simultaneous measurement of cortisol and ACTH improves the accuracy of diagnosis of primary adrenal failure:
 - Low** serum cortisol ($<200\text{nmol/L}$) and
 - High** plasma ACTH ($>200\text{ ng/L}$)

Confirmatory Tests

1. Short tetracosactrin (Synacthen) test (Short ACTH stimulation test)

- Measure basal S. cortisol
- Stimulate with I.M. synthetic ACTH (0.25 mg)
- Measure S. cortisol 30 min after I/M injection
- Normal: **↑ of S. cortisol** to **>500 nmol/L**
- Failure of S. cortisol to respond to stimulation, **confirm AD.**
- **Abnormal results:**
 - emotional stress
 - glucocorticoid therapy
 - estrogen contraceptives.

Confirmatory Tests

Cont'd

2. Adrenal antibodies

- Detection of adrenal antibodies in serum of patients with autoimmune Addison's disease

3. Imaging (Ultrasound/CT)

- Ultrasound or CT for adrenal glands for identifying the cause of primary adrenal failure

Investigation of Secondary AC Insufficiency

- **Low** serum cortisol with **low** plasma ACTH
- No response to short synacthen test: Adrenocortical cells fail to respond to short ACTH stimulation
- **Depot Synacthen test (confirmatory test)**
 1. Measure basal S. cortisol
 2. Stimulate with I.M. synthetic ACTH (1.0 mg) on each of three consecutive days
 3. Measure S. cortisol at 5 hours after I.M. injection on **each** of the three days

Investigation of Secondary AC Insufficiency

Depot Synacthen test Cont'd

Interpretation of results:

- **Addison's disease:** No rise of S. cortisol >600 nmol/L at 5 h after 3rd injection.
- **Secondary AC:** Stepwise increase in the S. cortisol after successive injections
- **Limitations:**
 - Hypothyroidism:** Thyroid deficiency must be corrected before testing of adrenocortical functions
 - Prolonged steroid therapy**

Investigation of Secondary AC Insufficiency Cont'd

Other Investigations

- **Insulin-induced hypoglycemia:**
Adrenal failure secondary to pituitary causes
- **MRI for pituitary gland**

Investigation for Addison's disease

Screening

- Basal plasma ACTH and basal serum cortisol, glucose, urea and electrolytes
- **High** ACTH and **Low** cortisol

Confirmation

- Short ACTH stimulation test: **No response**

Others

- Adrenal autoantibodies
- Ultrasound/CT adrenal glands

Investigation for Secondary AC Insufficiency

Screening

- **Low ACTH** and **Low cortisol**

Confirmation

- **Long ACTH stimulation test: Stepwise increase in S. cortisol**

Others

- **Insulin-induced hypoglycemia**
- **MRI pituitary gland**

Take home messages

- Addison's disease is due to destruction of adrenals by autoimmune, infection, or infiltrative lesions.
- Adrenocortical hypofunction may occur secondary to pituitary disease, e.g., tumors, infection, trauma, or iatrogenic (surgery or radiation).
- Initial screening for Addison's disease by serum cortisol and ACTH. Other tests to support the diagnosis include serum urea, electrolytes and glucose.
- Confirmatory tests for Addison's disease by short Synacthen test.
- Diagnosis of secondary adrenocortical hypofunction by depot (long) Synacthen test.

References

- Lecture notes, Clinical Biochemistry, Wiley BlackWell, 9th edition, 2013, chapter 9, page 116-133.
- Clinical Chemistry, Principles, Procedures, Correlations, Lippincott Williams & Wilkins, 7th edition, 2013, chapter 21, page 453-471.
- Lippincott's Illustrated Reviews: Biochemistry 6th edition, Unit III, Chapter 18, Pages 219-244.