Biochemistry of Addison's Disease

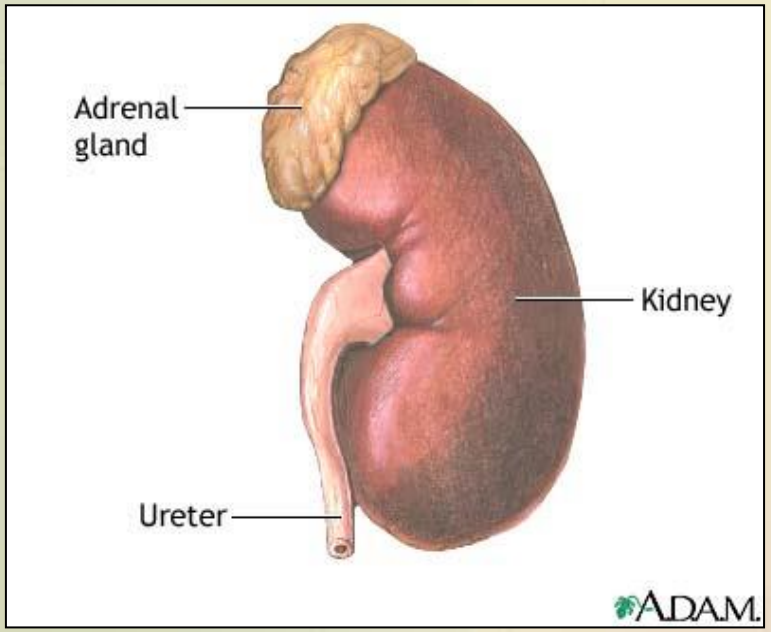
Endocrine Block

Objectives

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

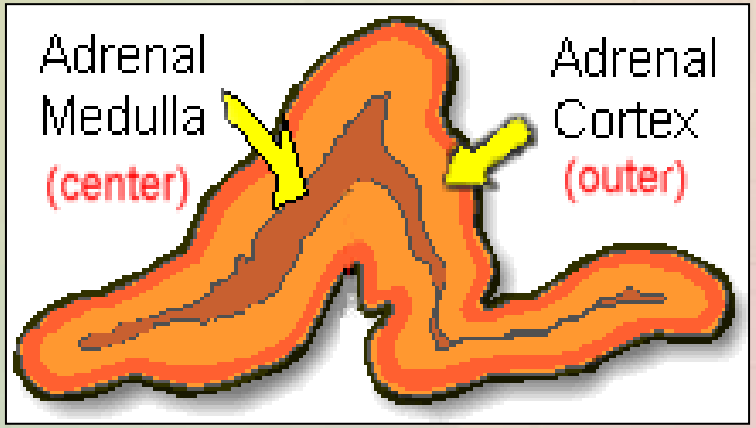
ANATOMICALLY:

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



HISTOLOGICALLY:

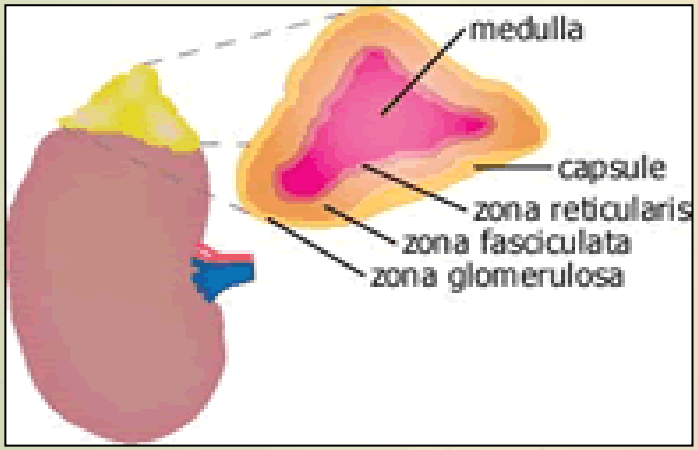
- The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla.



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

- Zona Glomerulosa

  The outermost zone → aldosterone (the principal mineralocorticoid).



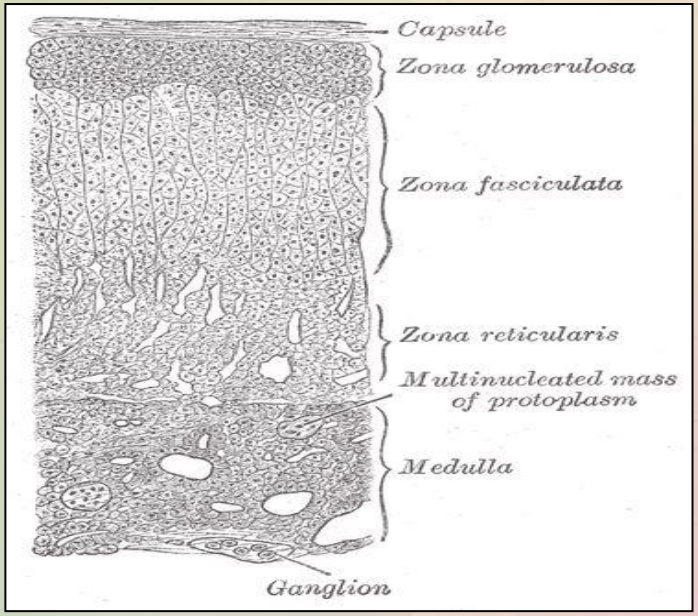
The deeper layers of the cortex:

- Zona Fasciculata

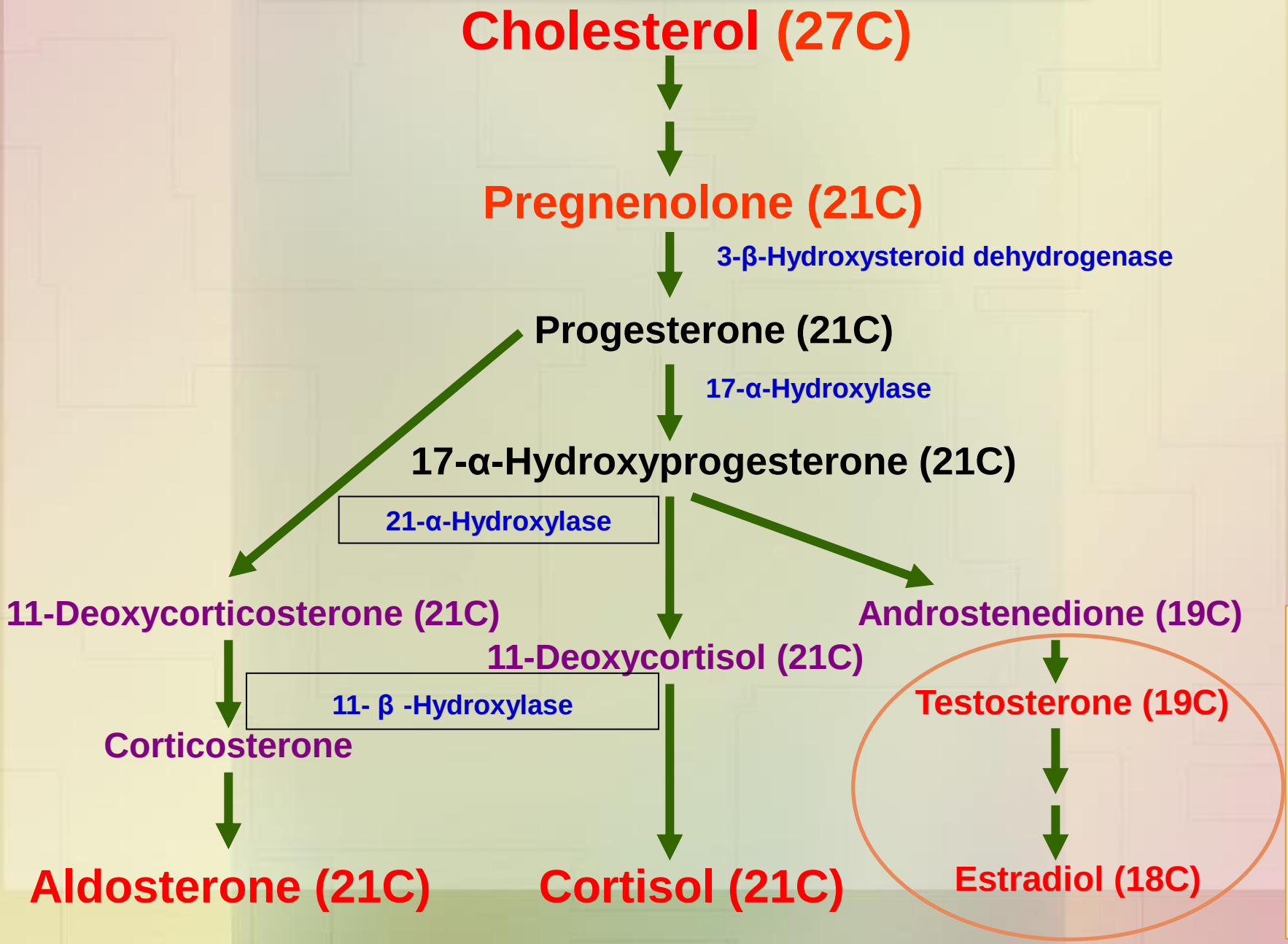
→ glucocorticoids – mainly cortisol (95%)

- Zona Reticularis

  → Sex hormones



Steroid Hormone Synthesis



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

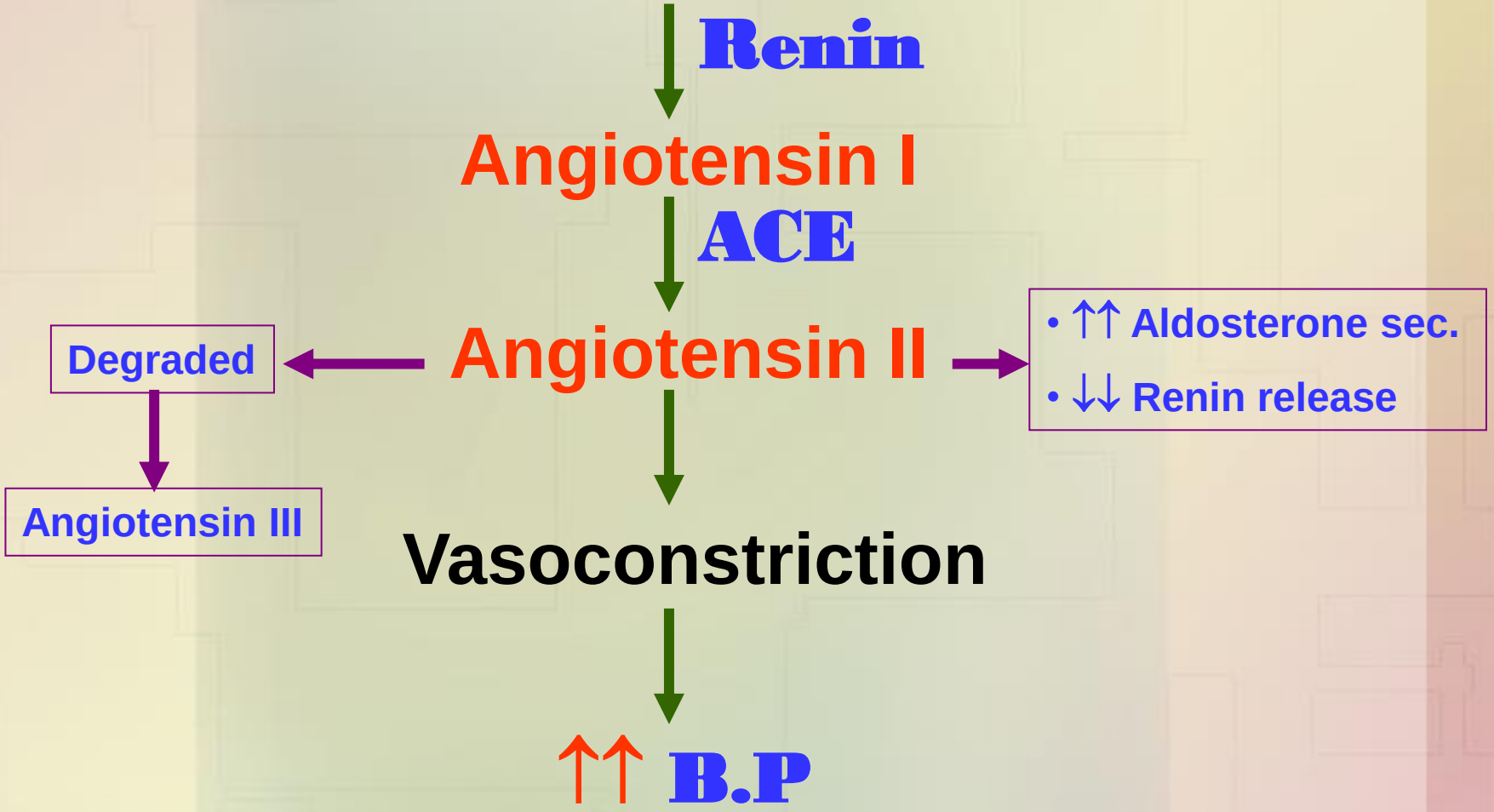
- It is the most important system controlling aldosterone secretion.
- It is involved in B.P. regulation.

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

(α2-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., amylodosis

B. Secondary AC hypofunction:

- Pituitary tumors
- Vascular lesions
- Head trauma
- Hypothalmic 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 (<200nmol/L) and

  High plasma ACTH (>200 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.