"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Addison's disease

Biochemistry Team 437

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Doctors slides
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Highlights

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Endocrine block

Objectives:

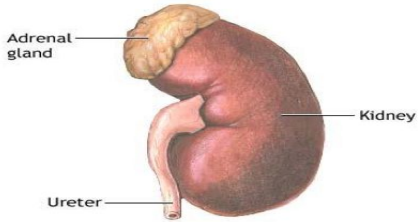
By the end of this lecture, students should be able to:

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

Adrenal Gland

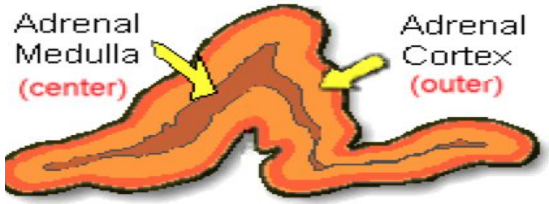
Anatomy

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



Histology

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

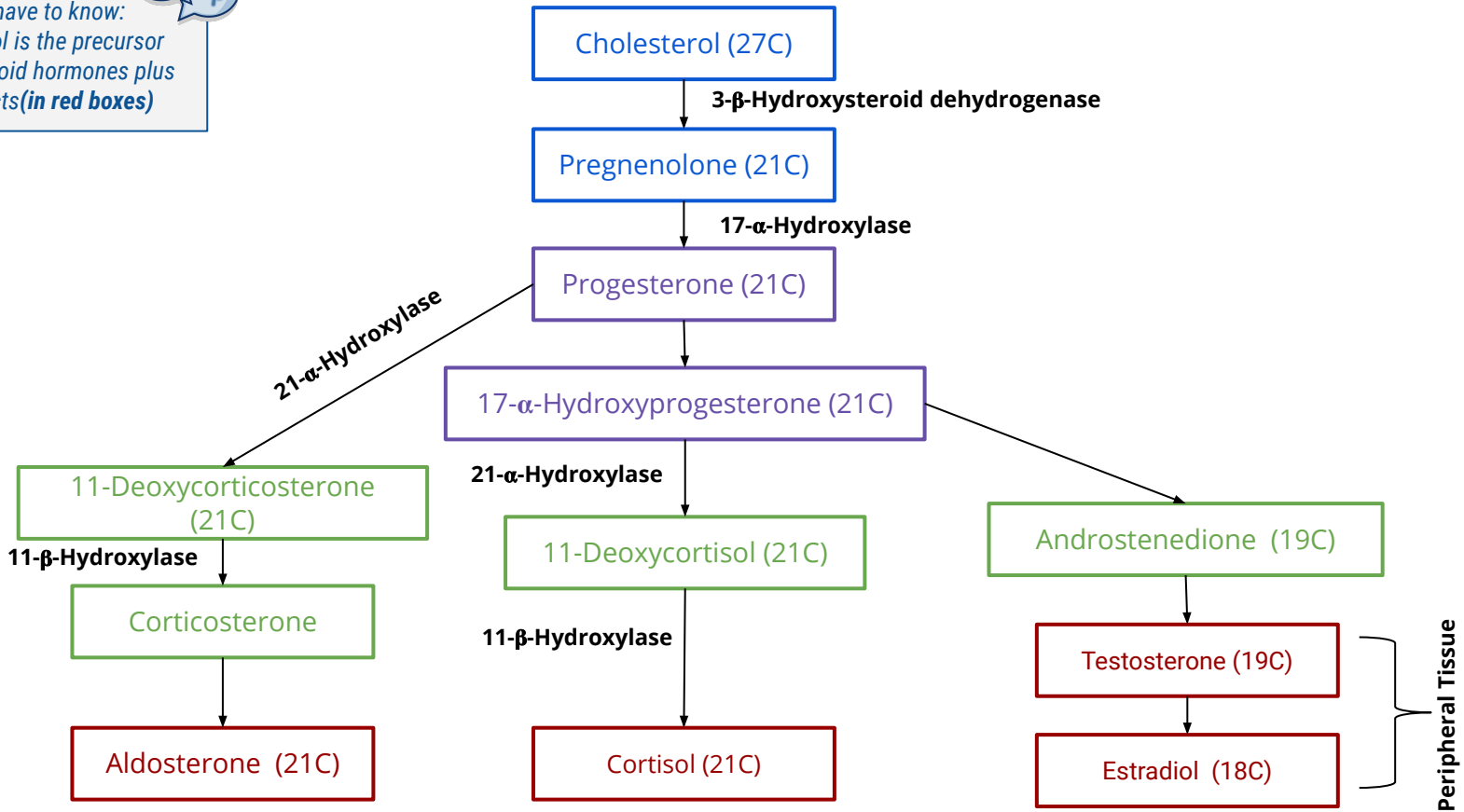


The adrenal cortex comprises three zones based on cell type and function:

Zona **G**lomerulosa	Zona **F**asciculata	Zona **R**eticularis
The outermost zone → aldosterone (the principal mineralocorticoid).	The deeper layer of the cortex → glucocorticoids – mainly cortisol (95%)	The deeper layer of the cortex → sex hormones
Aldosterone imbalances (HYPO is more common- Addisons)	Cortisol imbalances (HYPER is more common- Cushings)	

Steroid Hormone Synthesis

*What you have to know: Cholesterol is the precursor for all steroid hormones plus the products **(in red boxes)***



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.

-When you see aldosterone always think blood pressure!
*Also, Aldosterone acts on the collecting duct.

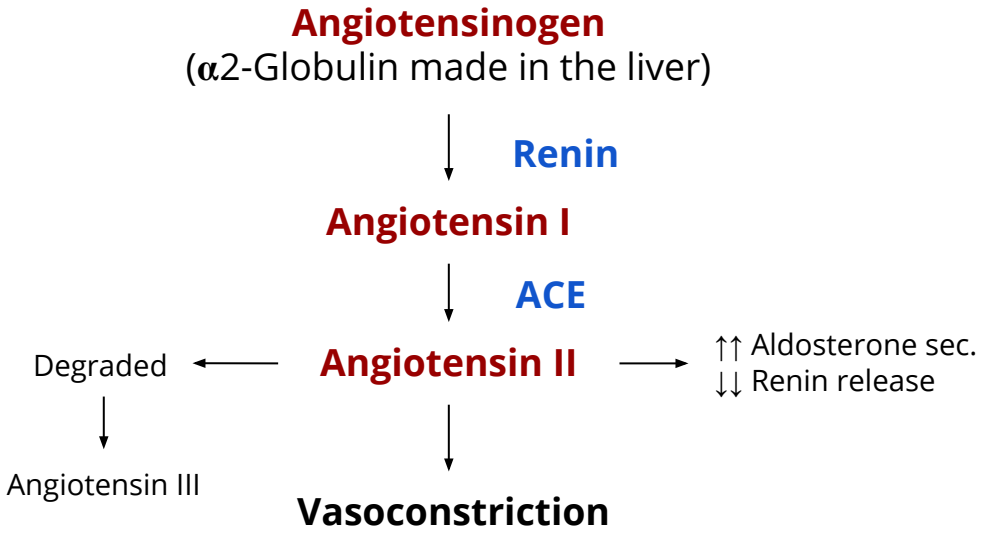
The Renin - Angiotensin System

- 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+

The Renin - Angiotensin System



- Patients with hypotension, will have low circulating blood volume which can be sensed by the baroreceptors of juxtaglomerular cells of the afferent arterioles, stimulating them to secrete renin.
- Renin is a proteolytic enzyme (Protein cleaving), it will cleave angiotensinogen into angiotensin I.
- And finally angiotensin I will be converted into angiotensin II, via ACE enzyme found mainly in the capillaries of the lung, but can also be found in the endothelium and epithelium of the kidneys
- ACTIVE angiotensin II seeks ultimately to increase blood pressure via two main mechanisms:

1. Stimulates aldosterone to reuptake sodium and water to increase blood volume
2. Vasoconstriction

- Aldosterone also has a negative feedback action on renin release

Adrenocortical Hypofunction (AC)

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Primary AC Hypofunction (destruction of adrenal gland; Addison's Disease)

Causes:

- Autoimmune
- Infection, e.g., tuberculosis
- Infiltrative lesions, e.g., amyloidosis

Signs & Symptoms:

(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 & mineralocorticoids
- Hypoglycemia, ↓Na+,↑K+ & raised urea
- Life threatening and need urgent care.

Secondary AC Hypofunction

Causes:

- Pituitary tumors
- Vascular lesions
- Head trauma
- Hypothalamic diseases
- Iatrogenic (steroid therapy, surgery or radiotherapy)

*Due to increase in ACTH, explained more next slide

- ***Remember:***
  - Primary: adrenal itself
  - Secondary: hypothalamic -pituitary axis / extra adrenal

Adrenocortical Hypofunction (AC)

Primary AC Hypofunction (destruction of adrenal gland; Addison's Disease)

Signs & Symptoms: 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*.

Remember it can be seen in patient with Cushing syndrome(ACTH dependent only).

Secondary AC Hypofunction

- In secondary adrenocortical insufficiency, skin darkening does not occur.

A part of ACTH, converts into MSH which increases the production of pigment from the melanocytes. When ACTH is high MSH will be high as well. Leading to skin darkening.

In primary adrenocortical insufficiency the adrenal gland does not secreted enough aldosterone, so positive feedback increases secretion of ACTH from the pituitary to compensate. Thus increasing ACTH. (ACTH high, MSH high, Aldosterone low)

But in secondary adrenocortical insufficiency, there is a insufficiency in ACTH leading to aldosterone insufficiency, therefor no excess MSH will be synthesized (ACTH low, MSH normal Aldosterone low)

Adrenocortical Hypofunction (AC) Investigations

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Primary AC Hypofunction (destruction of adrenal gland; Addison's Disease)

Investigation of Addison's disease :

- The patient should be hospitalized[1]
- Basal measurement of:
  - Serum urea, Na+, K+ & glucose
  - Serum cortisol and plasma ACTH
- Definitive diagnosis and confirmatory tests should be done later after crisis.
- Normal serum cortisol and UFC does not exclude AD[2]
- Simultaneous measurement of cortisol and ACTH improves the accuracy of diagnosis of primary adrenal failure:
  - Low serum cortisol (<200 nmol/L)
  - High plasma ACTH (>200 ng/L
- Next step is confirmatory tests "next slide"

Secondary AC Hypofunction

Investigation:

- 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) "slide 14"

Others:

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

1- Unlike Cushing, patients with addisons come to the emergency room with life threatening symptoms, so you take a small sample for screening but Before confirmatory tests are done you should treat the patient symptomatically

2- It is not enough to measure cortisol and ACTH one time, more than one low reading is required.

Confirmatory Tests of Addison's Disease

Short Tetracosactrin (synacthen) Test (short ACTH stimulation test)	Adrenal Antibodies	Imagining (Ultrasound/ CT)

• 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
	Detection of adrenal antibodies in serum of patients with autoimmune Addison's disease.	Ultrasound or CT for adrenal glands for identifying the cause of primary adrenal failure.

If we suspect something to be hypo → to test it we stimulate
- tetracosactrin (synacthen) is an active ACTH

Confirmatory Tests of Secondary AC Insufficiency

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Depot (prolonged) Synacthen 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

Interpretation of results:

Addison's disease:
No rise of S. cortisol >600 nmol/L at 5 hours after 3rd injection.

No rise because the adrenal gland doesn't work at all in addisons. No matter how much you try to stimulate it won't respond

Secondary AC:
Stepwise increase in the S. cortisol after successive injections

By stepwise we mean day by day

Limitations:

- Hypothyroidism: Thyroid deficiency must be corrected before testing of adrenocortical functions
- Prolonged steroid therapy

Doctor said they are not important

- Adrenal is atrophied because there is no ACTH or CRH secretion.
- Small amount of ACTH "short synacthen test" will not be effective in stimulating the adrenal gland.
- Continuous stimulation by depot synacthen test will stimulate the gland.

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الدكتور قال هذي اهم سلايد بالمحاضره!!!

VERY IMPORTANT!

	Addison's Disease	Secondary AC Insufficiency
Screening	- Basal plasma ACTH and basal serum cortisol, glucose, urea and electrolytes - High ACTH and low cortisol	Low ACTH and low cortisol
Confirmation	Short ACTH stimulation test: No response	Long ACTH stimulation test: Stepwise increase in S. cortisol
Others	- Adrenal autoantibodies - Ultrasound/CT adrenal glands	- Insulin-induced hypoglycemia - MRI pituitary gland

Summary

A. Aldosterone Hormone

- 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

B. Renin - Angiotensin System

- Most important regulatory mechanism for aldosterone secretion & BP regulation is involved
- Renin is a proteolytic enzyme produced by the juxtaglomerular cells of the afferent renal arterioles
  - Released in response to: ↓ blood volume, ↓ renal perfusion pressure & loss of Na+

C. Primary AC Hypofunction (Addison's Disease)

- Destruction of adrenal gland due to:
  - Autoimmune, Infection & Infiltrative lesions.
- Signs & symptoms:
  - Lethargy, weakness, nausea, weight loss postural hypotension, hyperpigmentation, deficiency of both glucocorticoids & mineralocorticoids, hypoglycemia, ↓Na+,↑K+ & raised urea

D. Secondary AC Hypofunction

- Caused by:
  - Pituitary tumors, vascular lesions, head trauma, hypothalamic diseases, & Iatrogenic
- Skin darkening (hyperpigmentation) doesn't occur

MCQs:

1- In response to increased levels of Angiotensin II, renin production and secretion
A. Increases
B. Decreases
C. Is not affected
D. Initially increases then decreases sharply

2- Which of the following is the confirmatory test for AD?
A. Adrenal autoantibodies
B. Basal plasma ACTH
C. MRI
D. Short ACTH stimulation test

3- A 55 year old patient came to the ER complaining of hyperpigmentation, hypotension, and weight loss. What is the most likely diagnosis?
A. Secondary AC hypofunction
B. AC hyperfunction
C. Primary AC hypofunction
D. None of the Above

4- Which one of the following can cause secondary AC hypofunction?
A. Head trauma
B. Tuberculosis
C. Autoimmune
D. None of the above

4- A
3- C
2- D
1- B

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Girls team

- العنود المنصور
- ليان المانع
- ارجوانة العقيل
- ريناد الغريبي

Boys team

Team leaders

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