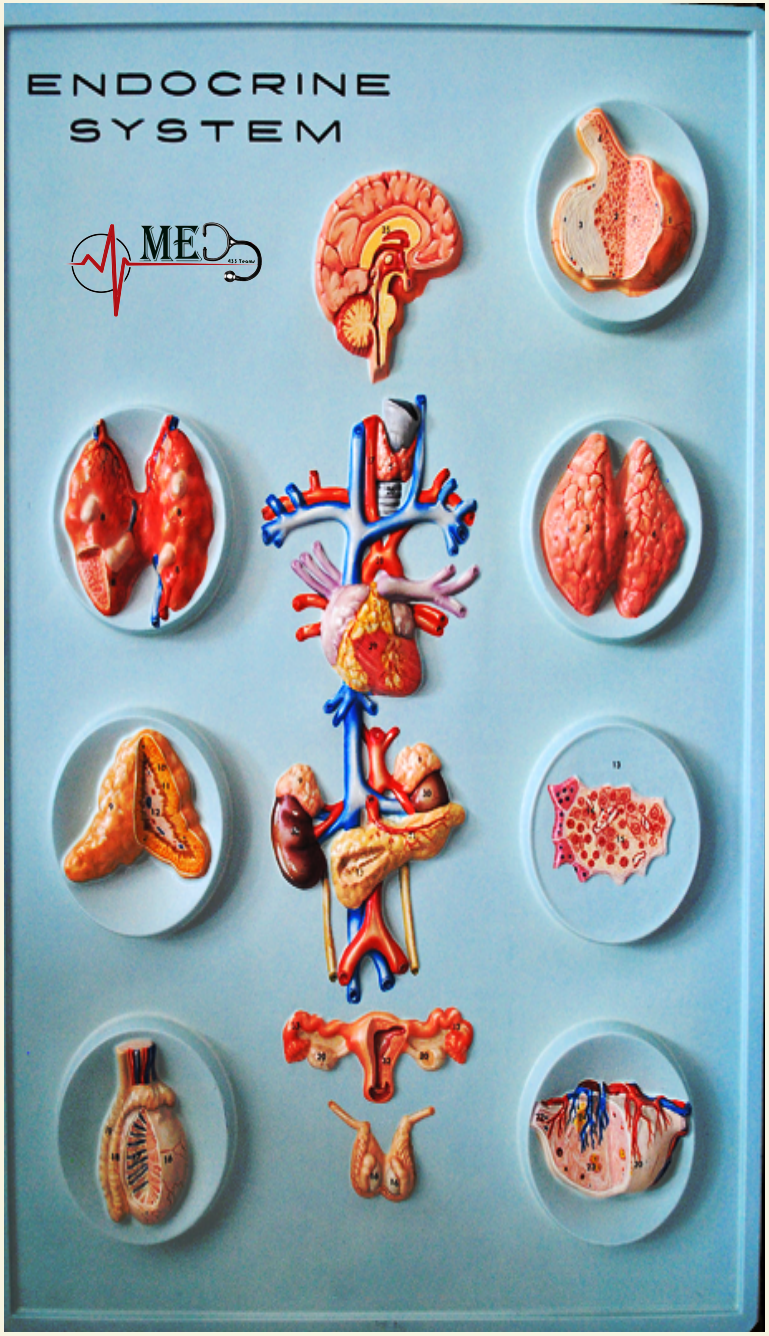


LECTURE 2 :

Biochemistry of Addison's Disease

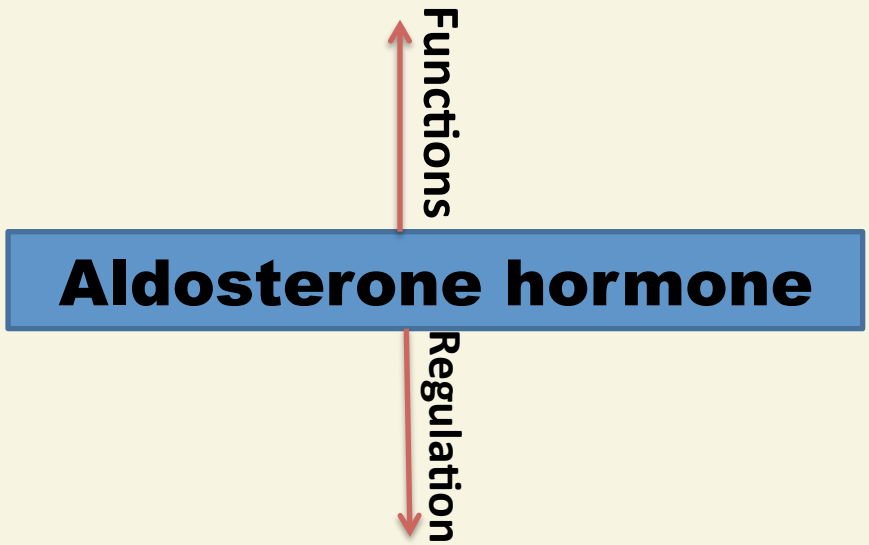
Objectives:

- 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

- major regulator of water and electrolyte balance, as well as blood pressure.
- act on the distal convoluted tubule of kidney, leading to:

↑↑ potassium excretion

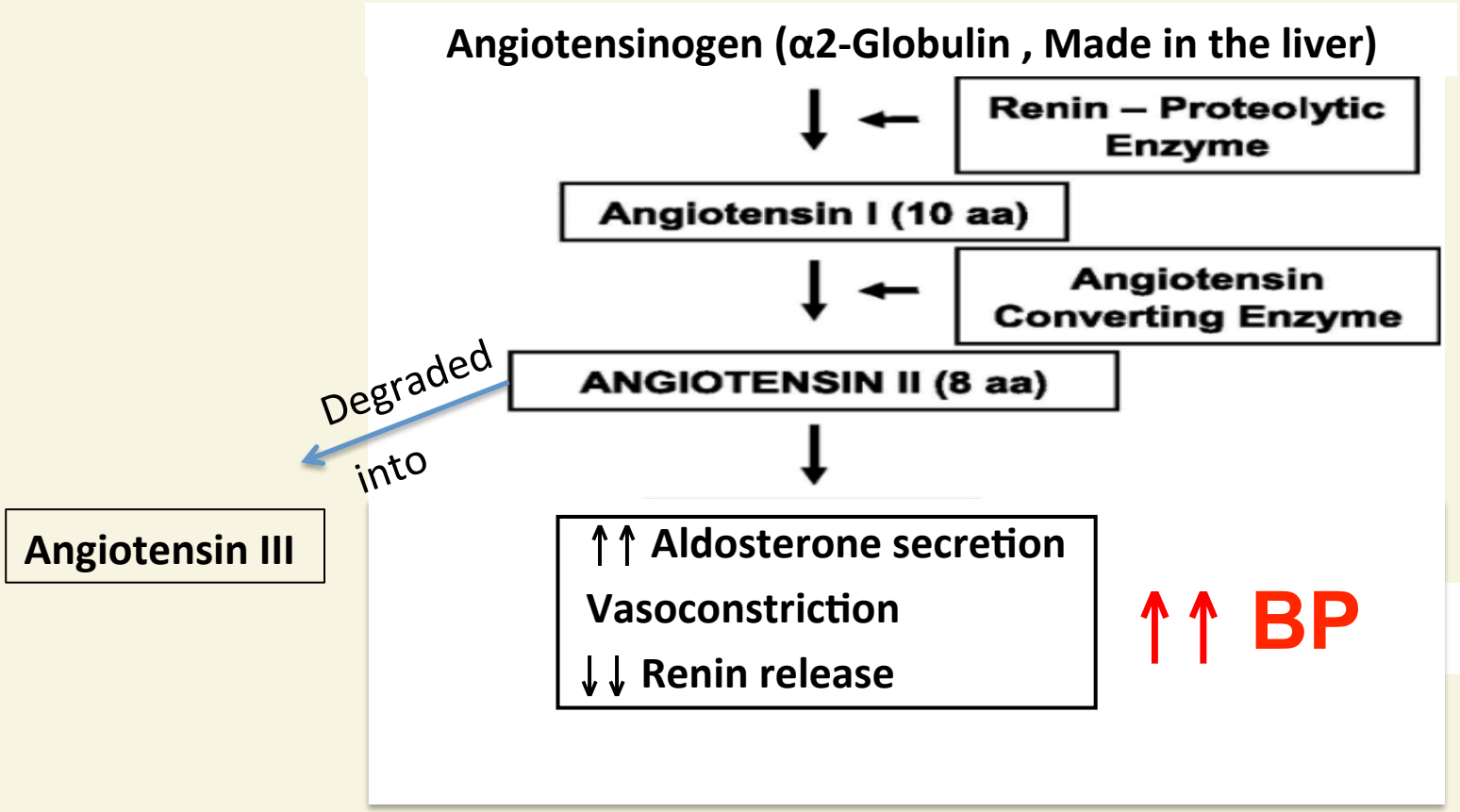
↑↑ Na and water reabsorption



Renin-Angiotensin system (RAS)

The most important regulatory mechanism for aldosterone secretion

It is involved in blood Pressure 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 :
  - ✓ ↓ Circulating blood volume.
  - ✓ ↓ Renal perfusion pressure.
  - ✓ Loss of Na^+.

Causes of adrenocortical hypofunction (AC)

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

- Autoimmune
- **Infection, e.g., tuberculosis**
- **Infiltrative lesions, e.g., amylodosis**

Secondary AC hypofunction:

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

SIGNS & SYMPTOMS OF AC HYPOFUNCTION

- Hyperpigmentation (buccal mucosa, skin creases, scars)
- ↑ K^+ , ↑ urea

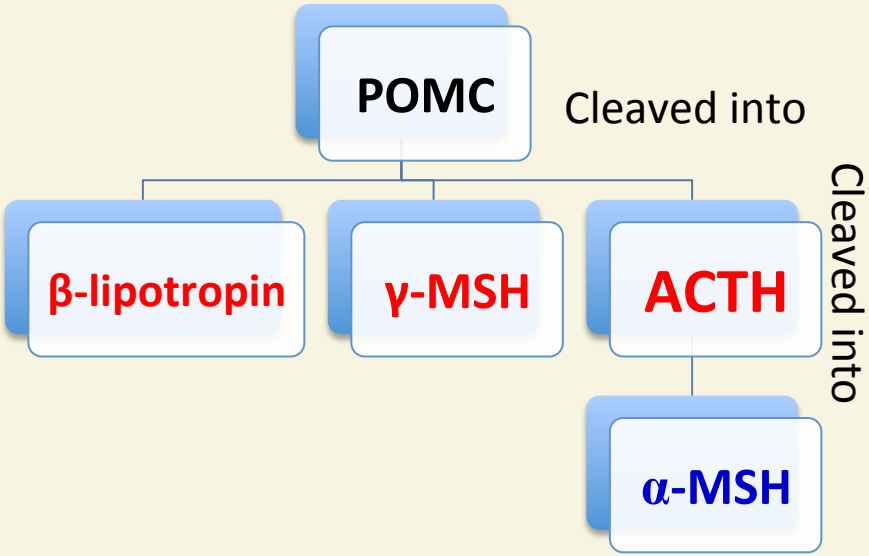
- Lethargy, weakness
- Nausea
- Weight loss
- Postural hypotension
- (Gluco, mineralocorticoids) Deficiency
- Hypoglycemia
- ↓ Na^+

WHY HYPERPIGMENTATION OCCURs ?

Because melanocyte-stimulating hormone (MSH) and (ACTH) share the same precursor molecule which is pro-opiomelanocortin (POMC).

α-MSH is the most important MSH for skin pigmentation.

In secondary adrenocortical insufficiency (NO ACTH), skin darkening does not occur.



Addison's disease (AD)

INVESTIGATIONS (screening)

Patient should be hospitalized

- Basal measurement of:
  1. Serum urea, Na^+, K^+ & glucose
  2. Serum cortisol and plasma ACTH
- Simultaneous measurement of cortisol and ACTH
  - **Low** serum cortisol (<200nmol/L)
  - **High** plasma ACTH (>200 ng/L)

Confirmatory tests

- **Short tetracosactrin (Synacthen) test[1]**
- **Adrenal antibodies**
- **Imaging (Ultrasound/CT)**

****Normal serum cortisol and urinary free cortisol (UFC) does not exclude AD.**

1: Tetracosactrin (commercial name: Synacthen) is a Synthetic ACTH

Confirmatory tests of Addison's disease

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

PROCEDURE

- Measure basal S. cortisol
- Stimulate with I.M. synthetic ACTH (0.25 mg)
- Measure S. cortisol 30 min after I/M injection

RESULTS:

- ✓ **Normal: ↑ of S. cortisol to >500 nmol/L**
- ✓ **Failure of S. cortisol to respond to stimulation, confirm AD.**

ABNORMAL RESULTS:

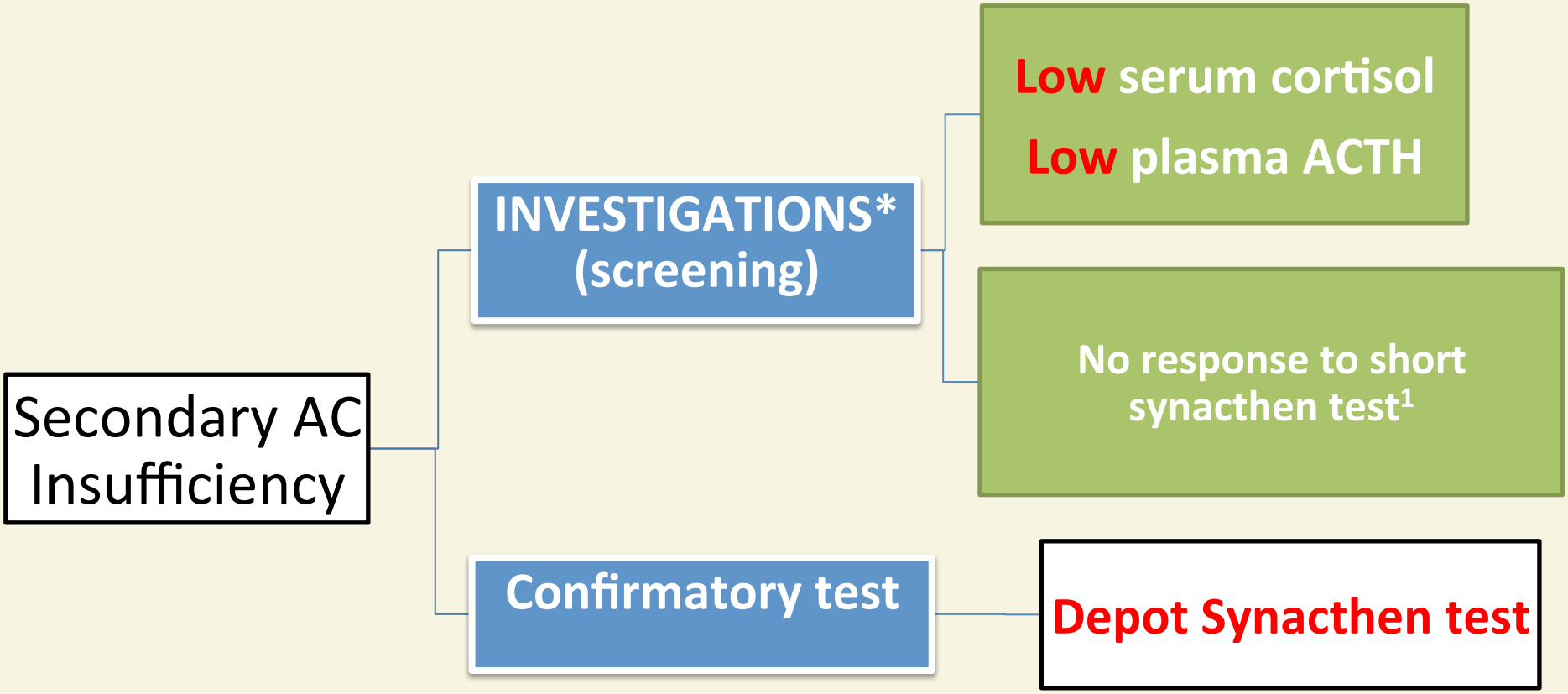
- Emotional stress
- Glucocorticoid therapy
- Estrogen contraceptives.

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



* Other investigations :

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

1: Adrenocortical cells fail to respond to short ACTH stimulation

Depot (long) Synacthen test
Confirmatory test

PROCEDURE

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 h after 3rd injection.

Secondary AC hypofunction:

Stepwise increase in the S. cortisol after successive injections

LIMITATIONS:

1. Hypothyroidism: must be corrected before testing of adrenocortical functions
2. Prolonged steroid therapy

Comparison	Primary AC hypofunction (Addison's disease)	Secondary AC hypofunction
Serum cortisol	LOW	LOW
Plasma ACTH	High (or normal)	LOW
Short ACTH stimulation test	No response	No response
Depot (long) Synacthen test	No response	Stepwise increase in the Serum cortisol
Gluco& meniralocorticoids	Deficient	Intact
Pigmentation	Yes	No

N.B : Hyperpigmentation is not only related to AC hypofunction, it occurs <u>whenever there is increased ACTH like</u> :

1. Primary AC hypofunction (Addison's disease)
2. ACTH-dependent AC Hyperfunction

Disease type	Primary adrenocortical hypofunction (Addison's disease)	Secondary adrenocortical hypofunction
Causes	• Autoimmune • Infection, e.g.: tuberculosis • Infiltrative lesions, e.g., amylodosis	• Pituitary tumors • Vascular lesions • Head trauma • Hypothalmic diseases • Iatrogenic (steroid therapy, surgery or radiotherapy)
Symptoms	• Lethargy, weakness, nausea & weight loss • Hypotension • Deficiency in glucocorticoids and mineralocorticoids • Increased ACTH (by –ve feedback) • Hyperpigmentation (increased ACTH contains increased MSH) • Hypoglycemia, hyponatremia and hyperkalemia	• Similar to Primary adrenocortical hypofunction symptoms, **ecxept:** ✓ Deficiency in ACTH ✓ NO hyperpigmentation (because there's a Deficiency in ACTH)
Screening investigations	• **High ACTH and Low cortisol**	• **Low ACTH and Low cortisol**
Confirmation investigations	• **Short Synacthen test:** It will shows no response on cortisol serum	• **Depot Synacthen test: :** Stepwise increase in cortisol serum
Other investigations	• **Adrenal autoantibodies** • **Ultrasound/CT of adrenal glands**	• **Insulin-induced hypoglycemia:** It will be no response due to ↓ ACTH • **MRI of pituitary gland**

TEST YOURSELF!

Q1 The principal physiological function of aldosterone is :

A. Na reabsorption
B. Na excretion
C. K and H excretion
D. Both A and C

Q2 the most important regulatory mechanism for aldosterone secretion:

A. Na and K reabsorption
B. Hypoglycemia
C. Heat loss
D. Renin-Angiotensin system

Q3 To confirm secondary AC hypofunction, we inject the patient with synthetic ACTH for .... days, on each day we measure his serum cortisol after ..... :

A. 3 ... 5 hours.
B. 5 ... 3 hours.
C. 3 ... 5 minutes

Q4 Angiotensin I is converts to Angiotensin II by:

A. Renin
B. Angiotensin converting enzyme (ACE)
C. Angiotensinogen
D. Aldosterone

Q5 The cause of hyperpigmentation in the primary adrenocortical insufficiency is?

A. ACTH stimulates melanin production
B. ACTH increase the sensitivity of MSH receptor.
C. ACTH and MSH share the same precursor

Q6 Why there's no hyperpigmentation in secondary adrenocortical hypofunction?

A. Due to elevated ACTH (which contains elevated MSH)
B. Due to decreased cortisol
C. Due to decreased ACTH (which contains decreased MSH)
D. Due to elevated cortisol

1-D 2-D 3-A 4-B 5-C 6-C

Q7 **A patient injected with short synthetic ACTH, then after 30 minutes we measured his serum cortisol and it was low however, his serum cortisol showed stepwise increase following injection with long Synacthen test. this result indicates:**

A. Primary AC hypofunction
B. Secondary AC hypofunction

Q8 **A cause of secondary adrenocortical hypofunction:**

A. Autoimmune
B. Pituitary tumors
C. Infection, e.g., tuberculosis
D. Infiltrative lesions, e.g., amylodosis

Q9 **Renin-Angiotensin system released into the circulation in response to :**

A. Hypertension
B. Hyperglycemia
C. Hypotension
D. Hypoglycemia

Q10 **The response in case of patient with secondary AC hypofunction injected with insulin is:**

A. Increase the cortisol level to compensate hypoglycemia
B. Hypoglycemia because there is destruction of the cells of the adrenal gland
C. Hypoglycemia because the pituitary gland lose the compensatory mechanism

7- B 8-B 9-C 10-C

THANK YOU ...

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