Important Doctors slides

Extra Information **Doctors notes**

[Editing file]

Biochemistry

Biochemistry of Addison's disease

"Your positive action combined with positive thinking results in success."
-Shiv Khera.

OBJECTIVES

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

Identify different causes of primary adreno-cortical hypofunction (Addison's disease)

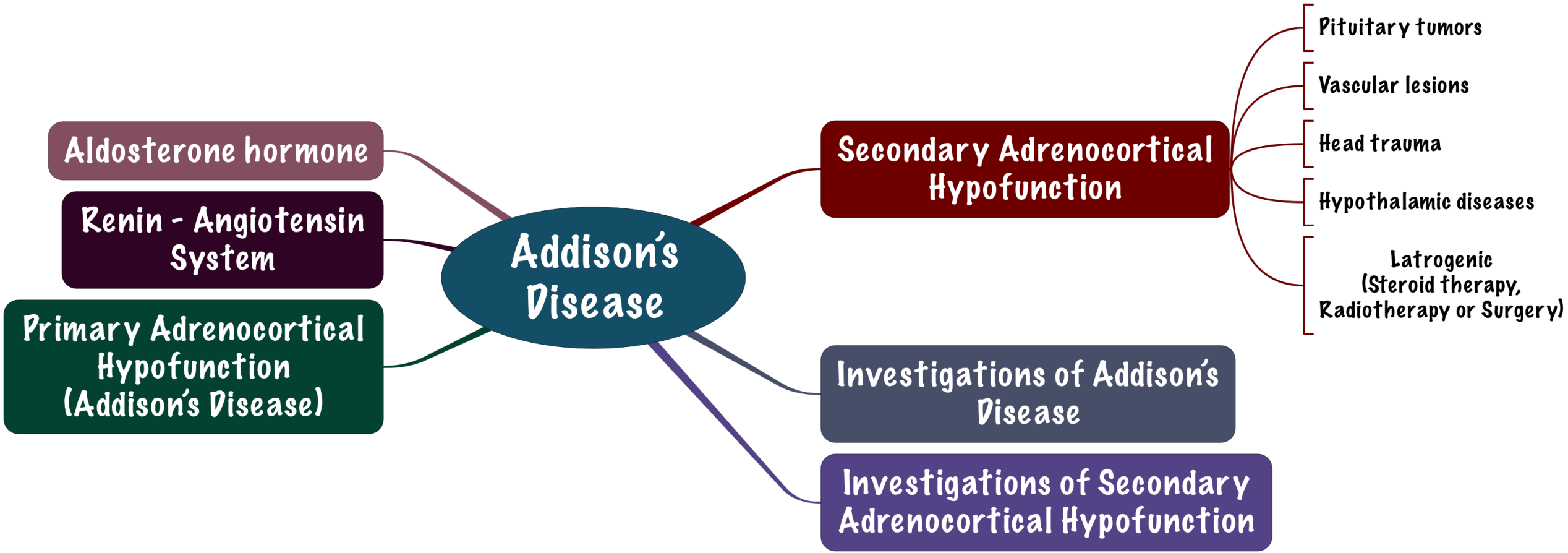
Identify secondary causes of adreno-cortical hypofunction

Understand the diagnostic algorithm for adreno-cortical hypofunction

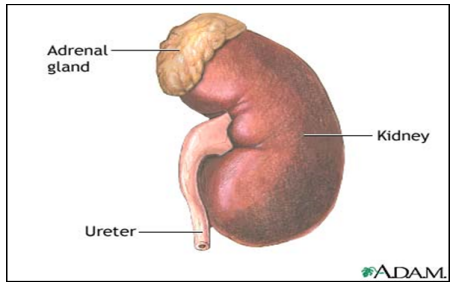
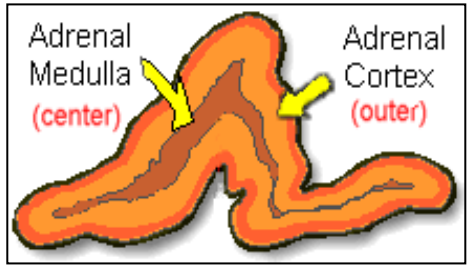
Understand the interpretation of laboratory tests of adreno-cortical hypofunction

Reference :

Overview


Addison's Disease
Aldosterone hormone
Renin - Angiotensin System
Primary Adrenocortical Hypofunction (Addison's Disease)
Secondary Adrenocortical Hypofunction
Pituitary tumors
Vascular lesions
Head trauma
Hypothalamic diseases
Latrogenic (Steroid therapy, Radiotherapy or Surgery)
Investigations of Addison's Disease
Investigations of Secondary Adrenocortical Hypofunction

Adrenal gland “ to understand better”

Anatomy	Histology
The adrenal gland is situated on the anteriosuperior aspect of the kidney	The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla.
	

Adrenal cortex zones based on cell type and function " to understand better"

Zona Glomerulosa

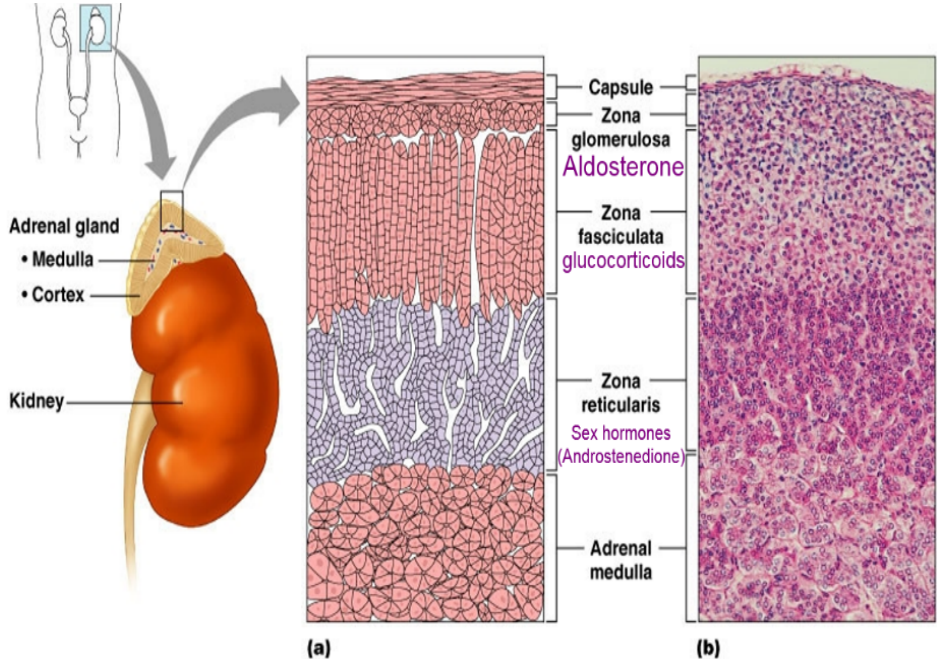
- The outermost zone
- Secrete aldosterone (the principal mineralocorticoid).

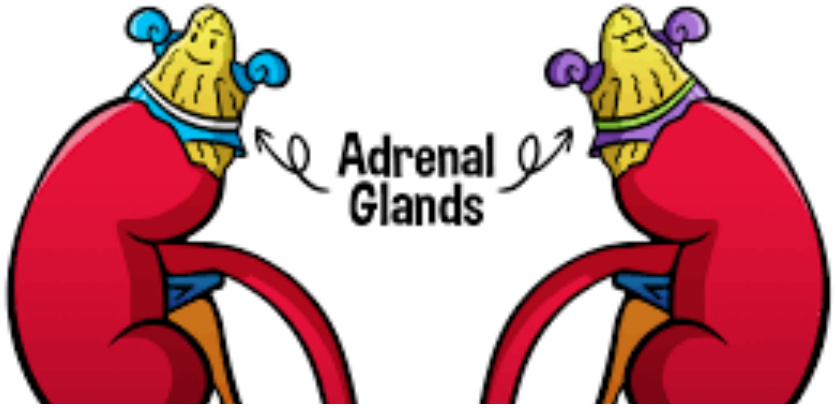
Zona Fasciculata

- Secrete glucocorticoids – mainly cortisol (95%)

Zona Reticularis

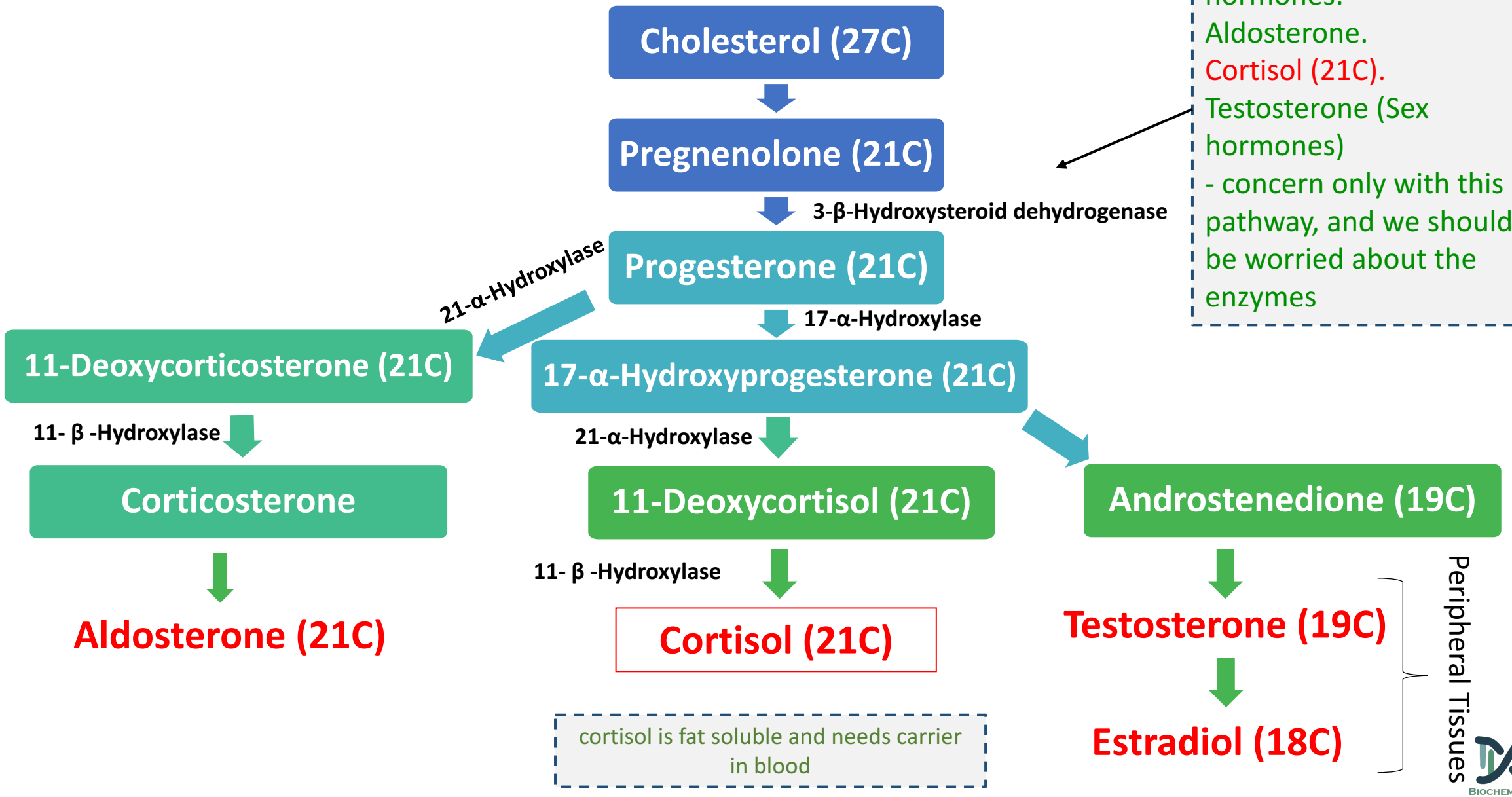
- Secrete Sex hormones, Mainly androgens





From outer to inner: GFR

Steroid Hormone Synthesis



- Just know that Cholesterol (27C) is the precursor of 6 hormones:
Aldosterone.
Cortisol (21C).
Testosterone (Sex hormones)
- concern only with this pathway, and we shouldn't be worried about the enzymes

cortisol is fat soluble and needs carrier in blood

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.

Reabsorption of Na+ will lead to water reabsorption that causes an increase in the blood volume and blood pressure.

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

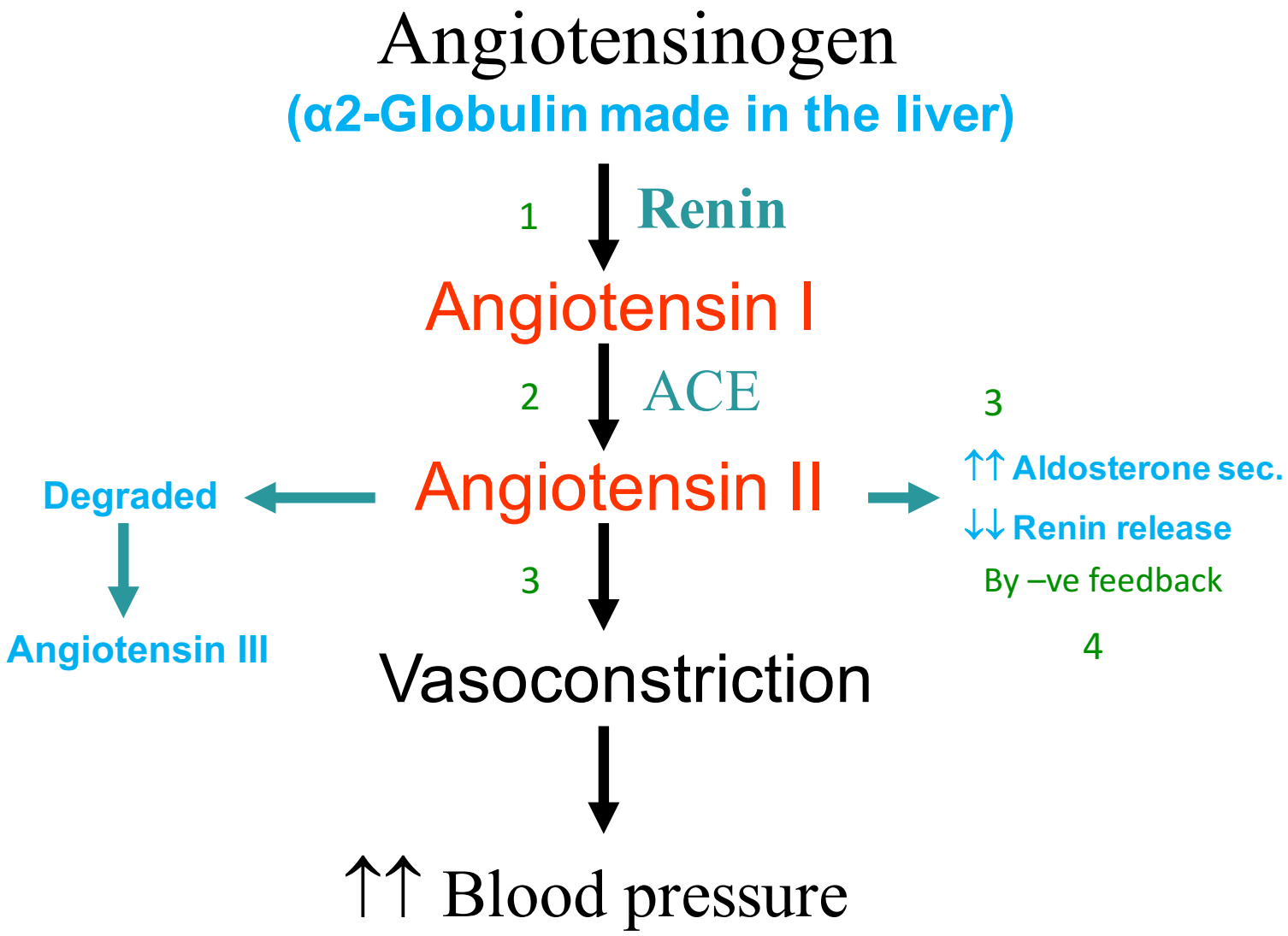
In Cushing we consider only the Cortisol but, in Addison's we consider both cortisol and aldosterone

So if we have low aldosterone, We will have low Na+ and water reabsorption and high K+ (hyponatremia and hypovolemia or hypotension)

Renin - Angiotensin System (RAAS system)

Renin - angiotensin system	
It is the most important system controlling aldosterone secretion. It is involved in B.P. regulation	
Renin	• a proteolytic (Breakdown the protein) enzyme produced by the juxtaglomerular cells of the afferent renal arteriole. ✓ Sensitive to B.P. changes through baroreceptors These juxtaglomerular cells contain baroreceptors on their surfaces which are sensitive to changes in blood pressure ✓ released into the circulation in response to : 1. a fall in circulating blood volume. 2. a fall in renal perfusion pressure. 3. loss of Na+. These conditions will activate the baroreceptors which leads to the stimulation of juxtaglomerular cells to release Renin.

Renin - Angiotensin System (RAAS system)



1. Renin is a proteolytic enzyme and not a hormone so its main function is to breakdown proteins into their active form as we can see here, Renin converts Angiotensinogen (inactive) into Angiotensin I (active)

2. Angiotensin I is converted into Angiotensin II by Angiotensin converting enzyme (ACE)

3. The Angiotensin II will increase the blood pressure by 2 ways:

A- by direct vasoconstriction since It has a vasoconstriction ability

B- By stimulating the release of aldosterone which increases blood pressure through Na+ and water reabsorption

4. When the aldosterone secretion is increased due to Renin -Angiotensin stimulation , there will be a decrease in the Renin release because the increase in blood pressure will inhibit the baroreceptors from releasing Renin from the juxtaglomerular cells

Causes of adrenocortical hypofunction (AC)

Primary AC hypofunction	Secondary AC hypofunction:
• Destruction of adrenal gland, Addison's disease • Due to: ✓ Autoimmune ✓ Infection, e.g., tuberculosis ✓ Infiltrative lesions, e.g., amylodosis	• Due to:- • Pituitary tumors • Vascular lesions • Head trauma • Hypothalmic diseases • Iatrogenic (steroid therapy, surgery or radiotherapy)
Problem in the adrenal gland	Problem in something other than adrenal gland but will affect the adrenal function

Signs and symptoms od Addison's disease

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), Because of Na loss
- Hyperpigmentation (buccal mucosa, skin creases, scars)
- Deficiency of both glucocorticoids and mineralocorticoids (Aldosterone)
- Hypoglycemia, decrease Na+, increase K+ and raised urea
- Life threatening and need urgent care.

patient with Addison disease will come with crisis and needs emergency (hypotension symptoms and especially on standing)

Investigation of Addison's disease (AD)

<table>
<tr><th colspan="2">Investigation of Addison's disease (AD)</th></tr>
<tr><td colspan="2">• The patient should be hospitalized. Because he has hypoglycemia (one of emergency conditions)
• Normal serum cortisol and UFC does not exclude AD. We have to do confirmatory test.
• Definitive diagnosis and confirmatory tests should be done later after crisis.
This means that first we treat the hypotension crises and other Addison symptoms then we do the confirmatory tests through investigations</td></tr>
<tr><td>Basal measurement of:</td><td>- Serum urea, Na^+, K^+ & glucose.
- Serum cortisol and plasma ACTH.</td></tr>
<tr><td>Simultaneous measurement of cortisol and ACTH improves the accuracy of diagnosis of primary adrenal failure:</td><td>• 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)
- In secondary both will be Low
- The ACTH is high because there is No negative feedback</td></tr>
</table>

Investigations 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.

ما رح تستجيب لل Synacthen test short ACTH لآن الـAdrenal gland صارت خاملة بسبب قلة ال ACTH لكن اذا أعطيناها جرعات من ال ACTH في ايام متتالية رح تبدأ تستجيب وتزيد ال cortisol في الدم وهذا هو Depot synacthen test confirmatory for secondary hypo AC insufficiency

Investigations of Secondary AC Insufficiency

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 We give him I.M injection 1 mg of synthetic ACTH and measure S. Cortisol after 5 hours from the injection, we do this procedure again for 3 days.	
Interpretation of results:	• **In Addison's disease (Primary):** No rise of S. cortisol >600 nmol/L at 5 h after 3rd injection. • **In Secondary AC:** Stepwise increase in the S. cortisol after successive injections. The level will increase more after each day of the 3 days.
Limitations	• **Hypothyroidism:** Thyroid deficiency must be corrected before testing of adrenocortical functions • **Prolonged steroid therapy**

Dr Rana says "I don't want you to know the limitations " Read it just in case.
And Dr. Mujammam said: it is very important So, We don't know ☺☺☺

Investigations of Secondary AC Insufficiency

❖ **Insulin-induced hypoglycemia:**

- To determine Adrenal failure secondary to pituitary causes.

❖ **MRI for pituitary gland**

Dr Rana says "most importantly you need to know the screening and confirmatory tests for Addison disease and secondary AC insufficiency "

- Short ACTH stimulation test (Addison disease)
- Depot synacthen test (Secondary AC insufficiency)

Summary

❖ Investigations of 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

❖ Investigations of 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

Hyper pigmentation 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.

Only in primary AC hypofunction there is skin hyperpigmentation because here the Adrenal cortex function is suppressed which causes a decrease in the release of its hormones (cortisol and aldosterone) this will stimulate the release of ACTH which is the precursor of POMC that is responsible for the hyperpigmentation when it is cleaved

In secondary AC hypo function, there won't be hyperpigmentation because ACTH release is decreased in the first place (the problem in pituitary)

Side note: Differentiate between Addison disease and Cushing disease
-Addison disease The problem is in the adrenal gland (primary)
-Cushing disease The problem is in the pituitary or higher (secondary)

Confirmatory Tests of Addison's disease (AD)

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. Because of failure in adrenal gland (primary).

❖ Abnormal results (imp!): We don't do the test to them	- Emotional stress. - Glucocorticoid therapy. - Estrogen contraceptives.

For this test we administer a synthetic ACTH intramuscularly.

In normal patients (normal AC function): They will have an increase in serum cortisol after 30 minutes of injection.

In patients with Addison disease : They will not have an increase in serum cortisol means they didn't respond to the ACTH stimulation test (because the problem in the adrenal gland itself) and that confirms the AD diagnosis.

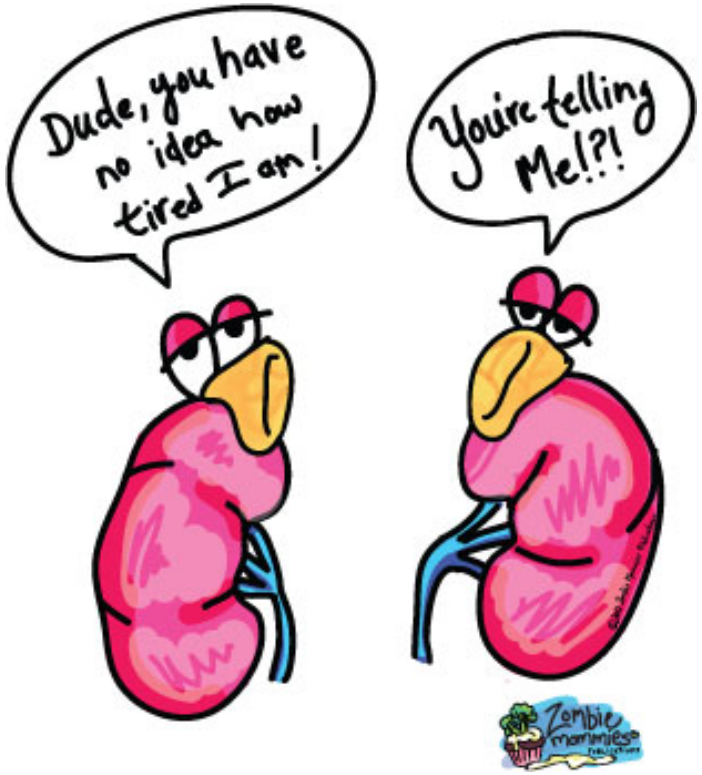
Confirmatory Tests of Addison's disease (AD)

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.



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.

Summary

Aldosterone Hormone	The renin - angiotensin system	Causes of adrenocortical hypofunction (AC)	Signs and symptoms of primary adrenal failure (Addison's disease)
• 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	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^+.	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)	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	Investigation of Addison's disease (AD)
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.	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. 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)

Summary

Confirmatory Tests			Investigation of Secondary AC Insufficiency	
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.	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	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 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	-Other Investigations Insulin-induced hypoglycemia: Adrenal failure secondary to pituitary causes MRI for pituitary gland

QUIZ

Q1 : Which of the following is the cause of hyperpigmentation in primary adrenocortical hypofunction?

A. ACTH stimulates melanin production
B. ACTH increases the sensitivity of MSH receptors
C. MSH & ACTH share the same precursor
D. ACTH stimulates discoloration of the skin by increased Vaseline production in the blood vessels.

Q2 : Which of the following is a cause of primary adrenocortical hypofunction?

A. Pituitary tumors
B. Head trauma
C. Steroid therapy
D. Amyloidosis

Q3 : Which one of the following is not used as a test for Addison's disease?

A. Short ACTH stimulation test
B. Insulin induced hypoglycemia
C. CT
D. Adrenal Antibodies

Q4 : Which of the following is a limitation to Depot Synacthen test?

A. Hypothyroidism
B. Hyperthyroidism
C. Short steroid therapy
D. Heart diseases

Q5 : Which of the following describes 2ry AC insufficiency?

A. High Serum cortisol & Normal Plasma ACTH
B. Low serum cortisol & sky high Plasma ACTH
C. Increased serum cortisol & Increased Urinary cortisol
D. Low serum cortisol with low plasma ACTH

Q6 : Which of the following is a confirmatory test for 2ry AC insufficiency?

A. Adrenal autoantibodies
B. Short ACTH stimulation test
C. Long ACTH stimulation test
D. Basal plasma ACTH

QUIZ

Q7 : 45 year old male came to your clinic.
He came because he has been feeling very weak lately.
He also mentioned that he feels nauseous and feels like he might collapse when he stands.

A) Mention 3 causes of Addison's disease.

1. Autoimmune
2. Infection: TB
3. Infiltrative lesions: amyloidosis

B) Mention 2 more symptoms of Addison's disease?

1. Hyperpigmentation
2. Weight loss
3. Hypoglycemia

C) Name 3 tests that are used to confirm the diagnosis of Addison's disease.

1. Short Synacthen (tetracosactrin) test (Short ACTH stimulation test)
2. Adrenal Antibodies
3. Imaging (CT, Ultrasound)

D) What are the limitations to the Depot synacthin test?

1. Hypothyroidism
2. Prolonged steroid therapy

Suggestions and recommendations

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

Biochemistry Team 436

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THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

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