Biochemistry of Addison's disease

Biochemistry Teamwork

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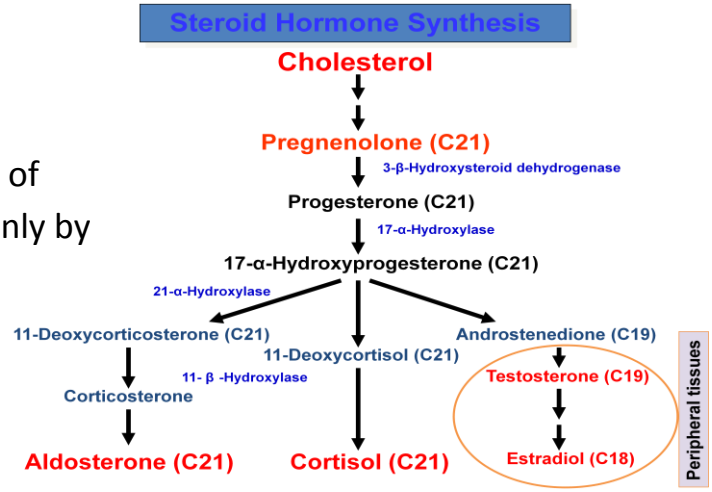
Red: important notes
Green: team's notes

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 tubules of kidneys, leads to:

- ↑↑ potassium excretion
- ↑↑ sodium and water reabsorption

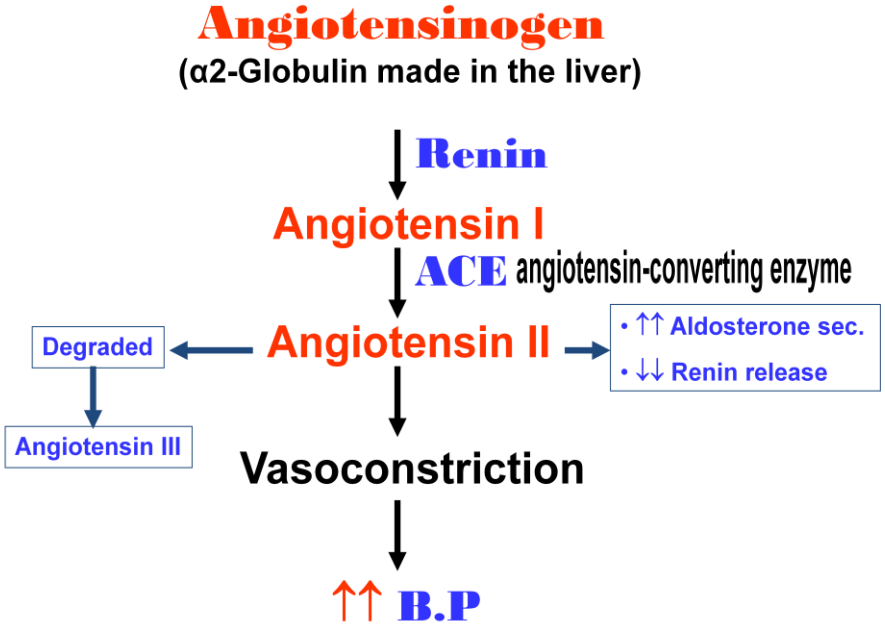
- Renin-Angiotensin Aldosterone System (RAAS) is the most important regulatory mechanism for aldosterone secretion

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^+.



CAUSES OF ADRENOCORTICAL HYPOFUNCTION:

A. Primary destruction of adrenal gland:

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

Amylodosis: is a progressive, incurable, metabolic disease characterized by abnormal deposits of protein in one or more organs or body systems.

B. Secondary to pituitary disease:

Anything affecting the central axis (pituitary-hypothalamus)

- Pituitary tumors
- Vascular lesions
- 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.
↑↑↑ **ACTH (because cortisol is low ➔ no negative feedback to pituitary ➔ secrete ACTH)**

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. **(Because ACTH is low)**

INVESTIGATION OF ADDISON'S DISEASE (AD): (primary)

- 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 (urinary free cortisol) do not exclude AD. (Because the patient might be in the initial stages of addison's and the cortisol reservoirs compensate for the lack of Cortisol synthesis)
- 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 (SST) (Short ACTH stimulation test)

Synacthen: synthetic analogue of ACTH.

- 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 (excludes hypofunction of adrenal gland)
- Failure of S. cortisol to respond to stimulation, confirms 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

INVESTIGATION OF SECONDARY AC (AdrenoCortical) 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):

- Measure basal S. cortisol
- Stimulate with I.M. synthetic ACTH (1.0 mg) on each of three consecutive days
- 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

INVESTIGATIONS FOR:

	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 (day by day) increase in S. cortisol
Others	• Adrenal autoantibodies • Ultrasound/CT adrenal glands	• Insulin-induced hypoglycemia • MRI pituitary gland

Questions:

Q1:One of the following is not a symptom of addison's disease.

A- Hypoglycemia

B- Hyponatremia

C- Hypokalemia

D- Hypochoremia

Q2: Restriction of sodium intake is commonly advised in :

A- Addison's disease

B- Diarrhoea

C- Hypertension

D- None of these

Q3: In Addison's disease, there is excessive retention of:

A- Potassium

B- Chloride

C- Sodium

D- Water

Q4: Which one of the following are features of secondary (central) AC insufficiency?

A- ↓ACTH - hypoglycemia - ↓ testosterone - normal aldosterone

B- ↑K^+ - metabolic acidosis - ↑H^+ - hypoglycemia

C- ↑ACTH - normal K^+ and H^+ - hyperglycemia - ↓blood pressure

D- ↑ ACTH - metabolic acidosis - ↓ aldosterone - ↓ blood pressure

Answers: C-C-A-A

Why is aldosterone normal in secondary AC insufficiency?

Because ACTH affects aldosterone secretion in a very minor way, the major effectors are RAAS and serum potassium. So when ACTH is low in secondary AC insufficiency the results of aldosterone would be Normal