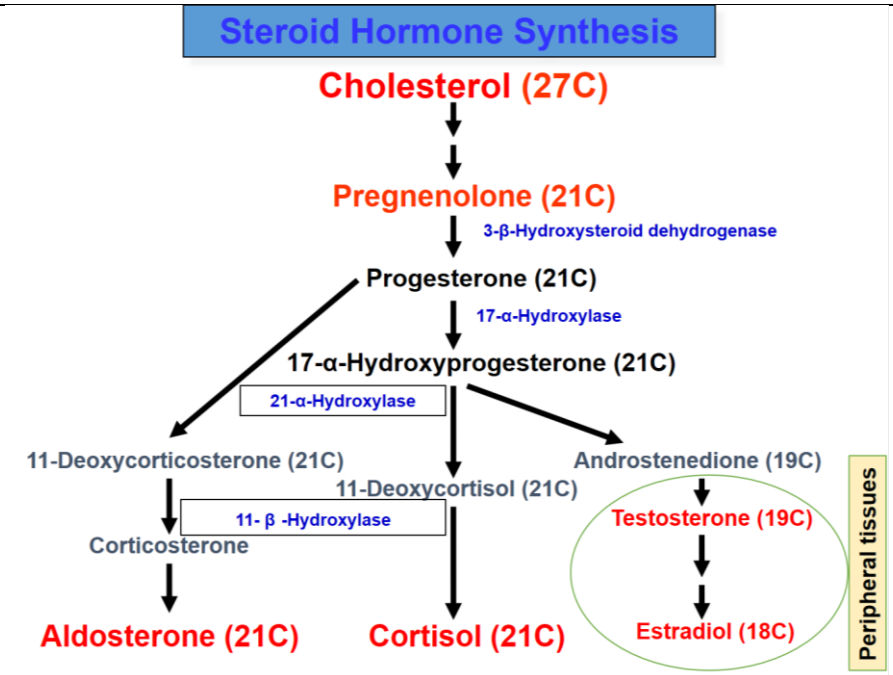
Addison's disease

Steroid Hormone Synthesis



Aldosterone Hormone

- The principal physiological function of aldosterone is to conserve Na^+, by acting on the distal convoluted tubule of kidney, mainly by:
  1. facilitating **Na^+ and water reabsorption**, and
  2. 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.

The renin - angiotensin system (RAS)

- Renin-Angiotensin system is the most important regulatory mechanism for **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^+.***
- *Role: converts Angiotensinogen (an α2-Globulin made in the liver) into Angiotensin I, which is then converted into Angiotensin II by ACE.*

Angiotensin II:

- *Role of Angiotensin II:*
- ↑↑ ***Aldosterone secretion***
- ↓↓ ***Renin release***
- *Vasoconstriction, thus* ↑↑ ***B.P***
- *Eventually Degraded into angiotensin III*

<table>
<tr><td>Causes of adrenocortical (AC) hypofunction</td><td>A. Primary AC hypofunction (Addison's disease):
Destruction of adrenal gland, due to:
• Autoimmune
• Infection, e.g., tuberculosis
• Infiltrative lesions, e.g., amylodosis</td><td>B. Secondary AC hypofunction:
• Pituitary tumors
• Vascular lesions
• Head trauma
• Hypothalmic diseases
• Iatrogenic (steroid therapy, surgery or radiotherapy)</td></tr>
<tr><td>Signs and symptoms of primary adrenal failure (AD)</td><td colspan="2">The symptoms are precipitated by <u>trauma, infection or surgery</u>:
• Lethargy, weakness, nausea & weight loss.
• Hypotension especially on standing (postural hypotension)
• Hyperpigmentation (buccal mucosa, skin creases, scars)
• Hypoglycemia, ↓ Na+, ↑ K+ and raised urea
• Life threatening and need urgent care.
• Deficiency of both glucocorticoids and mineralocorticoids
• Hyperpigmentation (buccal mucosa, skin creases, scars)</td></tr>
<tr><td>Hyperpigmentation in AD</td><td colspan="2">• Hyperpigmentation occurs because melanocyte-stimulating hormone (MSH) and (ACTH) share the same precursor molecule, Pro-opiomelanocortin (POMC).
• In 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.</td></tr>
<tr><td>Investigation of AD</td><td colspan="2">• Normal serum cortisol and UFC does not exclude AD.
• The patient should be hospitalized
• Definitive diagnosis and confirmatory tests should be done later after crisis.
• Screening:
Measurement of basal plasma ACTH and basal serum cortisol, glucose, urea and electrolytes (Na+ , K+)</td></tr>
<tr><td>1. Screening</td><td>Primary AC hypofunction:
Addison's disease (AD)
- <u>Simultaneous</u> measurement of cortisol and plasma ACTH improves the accuracy of diagnosis of primary adrenal failure: Low serum cortisol (<200nmol/L) and High plasma ACTH (>200 ng/L)</td><td>Secondary AC Insufficiency
- Low serum cortisol with low plasma ACTH.</td></tr>
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<table>
<tr><td rowspan="4">2. Confirmatory Tests</td><td colspan="3">Short tetracosactrin test (Short ACTH stimulation test)- Synacthen test</td></tr>
<tr><td>Procedure:</td><td>Results:</td><td>Abnormal results:</td></tr>
<tr><td>• Measure basal serum cortisol
• Stimulate with I.M. synthetic ACTH (0.25 mg)
• Measure S. cortisol 30 min after I.M. injection</td><td>Normal result: ↑ of S. cortisol to >500 nmol/L

In AD: Failure of S. cortisol to respond to stimulation, confirm AD.

In secondary AC insufficiency: No response (Adrenocortical cells fail to respond to short ACTH stimulation)</td><td>• emotional stress
• glucocorticoid therapy
• estrogen contraceptives.</td></tr>
<tr><td colspan="3">Long ACTH stimulation test- Depot Synacthen test:</td></tr>
<tr><td></td><td>Procedure:</td><td>Interpretation of results:</td><td>Limitations:</td></tr>
<tr><td></td><td>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</td><td>- 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</td><td>– Hypothyroidism: Thyroid deficiency must be corrected before testing of adrenocortical functions
– Prolonged steroid therapy</td></tr>
<tr><td rowspan="3">3. Other investigations</td><td colspan="2">Addison’s disease</td><td>Secondary AC Insufficiency</td></tr>
<tr><td colspan="2">Adrenal antibodies
• Detection of adrenal antibodies in serum of patients with autoimmune Addison’s disease</td><td>Insulin-induced hypoglycemia:
• Adrenal failure secondary to pituitary causes</td></tr>
<tr><td colspan="2">Imaging:
• Ultrasound or CT for adrenal glands for identifying the cause of primary adrenal failure</td><td>Imaging:
• MRI for pituitary gland</td></tr>
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