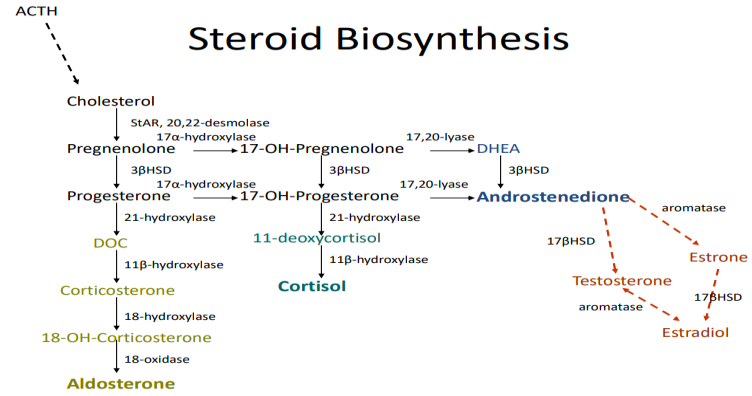
6 Adrenal Disorders

Adrenal Cortex

Zona Glomerulosa: Mineralocorticoids 5-10%
Zona Fasiculata: Glucocorticoids 75%
Zona Reticularis: Androgens

Function of the adrenal cortex

• Cholesterol is the starting point for all steroid hormone biosynthesis.
• It is obtained mostly from circulating LDL.
• It is modified by a series of hydroxylation reactions.
• The substrates have to move around the cell for the process of steroidogenesis to be complete as the the enzymes are in both the mitochondria and the endoplasmic reticulum.



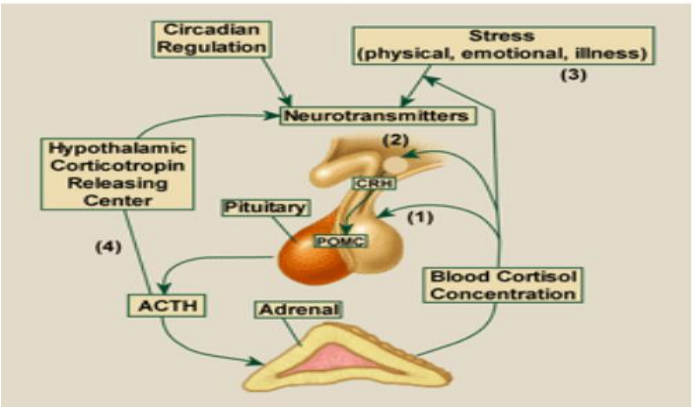
Regulation of steroidogenesis

• Hypothalamo-pituitary-adrenal axis:
- Cortisol is secreted in response to ACTH, which is stimulated mainly by CRH and to lesser extent AVP!
- ACTH is derived from proopiomelanocortin (POMC).
- ACTH stimulates the production of LDL receptors and the uptake of LDL. Diurnal rhythms of ACT.

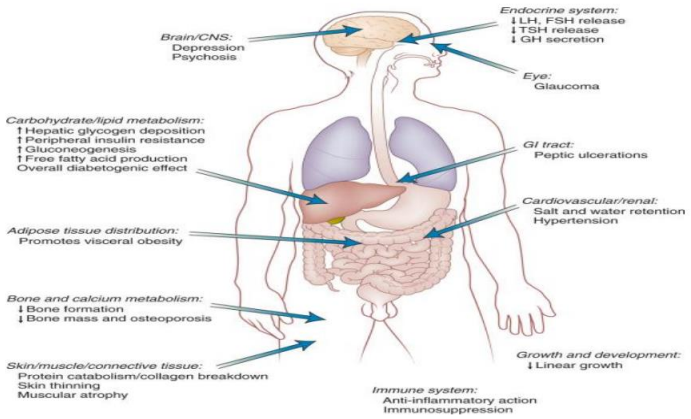
Diurnal rhythms of ACTH and cortisol

• CRH hypothalamic content peaks at about 4.00 am
• Peak plasma ACTH are seen at 4.00-6.00 am
• Peak plasma level of cortisol follows at 8.00 am
• ACTH and Cortisol are released in pulses each 30-120 minutes.
• This starts at the age of 6-12 months ,well established at 3 years.

Adrenal physiology 1: HPA axis



Physiology of GCs



Transporting cortisol

• 80% is bound to corticosteroid binding globulin(transcortin) in plasma.
• 15% to albumin.
• Transcortin does not bind dexamethasone.
• When the concentration of the binding globulin increases, the total concentration of the hormone in plasma increases.

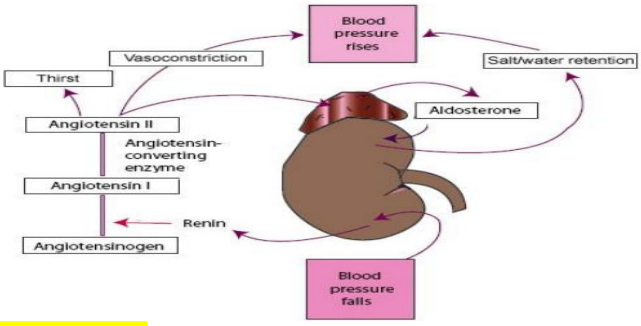
Zona glomerulosa

• Aldosterone is the main product.
• Acts on distal tubules and collecting ducts ,increases Na reabsorption.
• Raises blood pressure by increasing plasma volume and increasing the sensitivity of the artriolar muscles to vasoconstrictor agents.
• Present in lower concentrations and is cleared more rapidly than cortisol but is still responsible for 80% of the mineralocorticosteroid activity of the adrenal gland secretion.

Regulation of aldosterone secretion

• The renin angiotensin system is the most important regulator.
• ACTH deficiency does not alter aldosterone production.

Adrenal physiology 2: Renin-angiotensin system



Zona reticularis

• Secretes DHEA, DHEAS, and androstendione.
• Can be converted peripherally to testosterone.
• Can not on their own activate androgen receptors.
• Secreted in large amounts in fetal and newborn period.
• Then it goes into rest till 7-8 years old , then adrenarche.
• It reaches a peak in young adulthood and then wanes down gradually.
• ACTH plays a permissive role in adrenarche but is not the only player.

Catabolism of Steroids

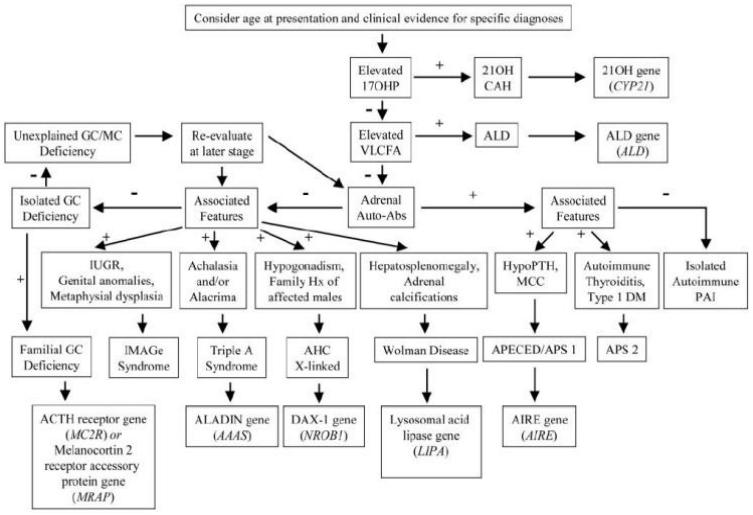
• <1% of plamsa cortisol and aldosterone are excreted unchanged in urine.
• 99% are metabolized by the liver before excretion through the kidneys. -adding OH groups or linkage to sulfate or glucuronide moieties renders steroids more water soluble.
• 24-hour urine samples to study the steroid hormone profile by MS -diagnostic tool-BUT analysis can be tough and needs lots of experience!

Causes of Adrenal Insufficiency

Primary Adrenal Insufficiency:
• Autoimmune adrenalitis
• Autoimmune polyglandular syndromes (type I and II)
• Tuberculosis, fungal infections
• Sepsis
• AIDS
• CAH
• Adrenal hemorrhage or infarction
• Cong. adrenal hypoplasia
• Adrenoleukodystrophy (and other metabolic disorders)
• Primary xanthomatosis
• Unresponsiveness to adrenocorticotropic hormone

Secondary Adrenal Insufficiency:
• Withdrawal from glucocorticoid therapy
• Hypopituitarism
• Hypothalamic tumors
• Irradiation or surgery of the central nervous system
• Defects in POMC synthesis or processing

Primary adrenal insufficiency in children:Suggested diagnostic algorithm



Primary adrenal insufficiency: Etiologies

Acquired
- Autoimmune
- AIDS
- Tuberculosis
- Bilateral injury
  - Hemorrhage
  - Necrosis
  - Metastasis
- Idiopathic

Congenital
- Congenital adrenal hyperplasia
- Wolman disease
- Adrenal hypoplasia congenita
- Allgrove syndrome (AAA)

Syndromes
- Adrenoleukodystrophy
- Kearns-Sayre
- Autoimmune polyglandular syndrome 1 (APS1)
- APS2

Addison's Disease

• 1 st described in 1855 by Dr. Thomas Addison
• Refers to acquired primary adrenal insufficiency
• Does not confer specific etiology – Usually autoimmune (~80%).

Primary adrenal insufficiency

Symptoms:
1. Fatigue
2. Weakness
3. Orthostatsis
4. Weight loss
5. Poor appetite
6. Neuropsychiatric – Apathy – Confusion
7. Nausea, vomiting
8. Abdominal pain
9. Salt craving

Physical findings:
1. Hyperpigmentation
2. Hypotension
3. Orthostatic changes
4. Weak pulses
5. Shock
6. Loss of axillary/pubic hair (women)

Laboratory findings:
1. Hyponatremia
2. Hyperkalemia
3. Hypoglycemia
4. Narrow cardiac silhouette on CXR
5. Low voltage EKG

Evaluation:
1. 0800 cortisol level
2. ACTH level
3. Random cortisol in ill patient
4. ACTH stimulation test
5. Suspected CAH Needs special evaluation
6. Renin and serum lytes
7. Adrenal Autoantibodies
   - ACA—adrenal cortex antibody
   - Anti-21-OH-hydroxylase antibody
8. Imaging
9. Urine collection and steroid analysis for metabolites.
10. Genetic testing

ACTH Stimulation:
• <u>Low dose (1 mcg) test</u>
1. Baseline and 30 minute cortisol levels
2. More physiological ACTH level/stimulation
3. Useful in central AI
4. Useful for assessing recovery after chronic steroid treatment

• <u>High dose (250 mcg) test</u>
1. Baseline, 30 and 60 minute levels
2. Stronger stimulation than 1 mcg test
3. 17OHP
4. insulin/hypoglycemia test

Treatment:
• Stress dosing. • Maintainance. • Medical alerts.

Stress dose steroids:

1. Loading dose
   - 50-100 mg/M2 hydrocortisone IV/IM
   - Small/medium/large approach
     - Infants: Hydrocortisone 25 mg
     - Small children: Hydrocortisone 50 mg
     - Larger children/teens: Hydrocortisone 100 mg
1. Continue hydrocortisone with 50-100 mg/M2/day
   - Divide q6-8 hours
   - May be 2-3x home dose

Long term treatment:

1. Daily glucocorticoid replacement (hydrocortisone)
   - 10-15 mg/m2/day divided TID
   - Option to change to prednisone in teen years
2. Daily mineralocorticoid replacement
   - Fludrocortisone 0.05-0.2 mg daily
3. Patient education
   - Stress coverage
   - Emergency steroid administration:
     >IM hydrocortisone (Solucortef Actovial)
   - Medic Alert ID

Relative Steroid Potencies

	Glucocorticoid	Mineralocorticoid
Hydrocortisone	1	++
Prednisone/ Prednisolone	3-5	+
Methylprednisone	5-6	0
Dexamethasone	25-50	0
Fludrocortisone	15-20	+++++

Follow up:

2. Serum electrolytes
3. Renin
4. ACTH
5. 17OHP
6. Androgens
7. Bone age
8. Growth charts
9.

Refer to slide 22, 23.

21-hydroxylase deficiency CAH

• **Classification based on enzyme activity**:

1. Classic
   - Salt wasting (Complete deficiency)
   - Simple virilizing (Significant but partial defect)
2. Non Classic
   - Elevated enzyme levels (Mild deficiency)

Adrenal crisis

1. **IV fluids**: boluses then maint. And deficit according to the severity of dehydration,during which close monitoring of blood gas and lytes.
2. **Steroid replacement**: bolus then maint.,then shift to oral.
3. **Hypoglycemia**: 2 ml/kg 10%dextrose bolus.
4. **Hyperkalemia**: usually normalize with fluids and steroid stress dose.
5. Continue…

5. If k^+ **>6**mmol/L **cardiac monitor**.
6. If k^+ **7**mmol/L either **ca-gluconate** or **insulin with glucose IV**.

Cushing syndrome

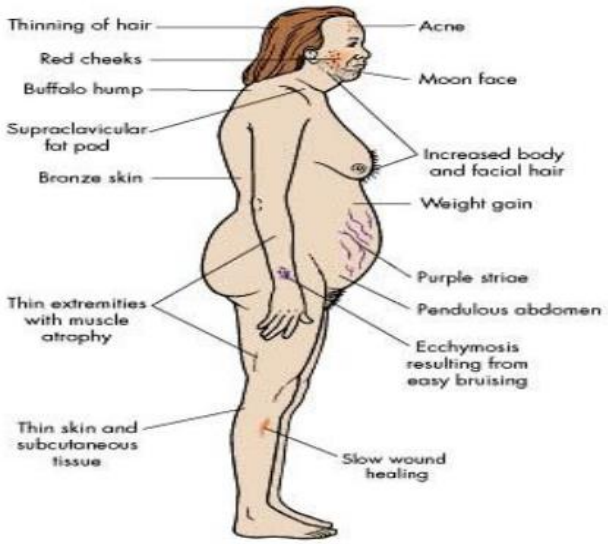
• **Hypercorticolism** due to pituitary overproduction of ACTH is cushing disease.
• Any other overproduction ACTH is ectopic ACTH syndrome.
• **Causes**:

1. **adrenal adenoma, carcinoma** or **multinodular adrenal hyperplasia**, mostly in infants and children < 7 yrs.
2. Iatrogenic cushing syndrome.

•**Clinical findings**:

1. Hairsutism
2. Facial flushing
3. Striae
4. Hypertension
5. Muscular weakness
6. Buffalo hump
7. Psychological disturbances
8. Mostly seen in adults or late presentation in childhood.
9. Obesity (that starts generalised) and GROWTH ARREST are the important initial and alarming signs.
10. Bone undermineralization.
11. Puberty arrest.
12. Compulsive behavior.
13. In carcinomas and ectopic forms have a more fuminant coarse.

• In children, awell defined microadenoma in 80-85% of cases.
• **Treatment** is with **trans-sphenoidal surgery**.
• Minority will have high CRH, which is difficult to distinguish from 1ry pit. Adenoma.



Other causes of Cushing syndrome

1. Ectopic ACTH secretion: oat cell carcinoma. carcinoid, pancreatic islet cell carcinoma and thymoma. mostly in adults but maybe seen in infants with neuroblastoma.
2. ACTH level 10-100 times in Cushing disease.
3. ACTH is not suppressed by dexamethasone suppression test.

Adrenal tumors

- More common in young children
- Adenomas secrete mainly cortisol ,minimal MCT and androgens.
- Carcinomas and nodular hyperplasia secrete cortisol and androgens.
- **Diagnosis:**
    1. Cortisol 8 am and 8 pm
    2. ACTH
    3. 24 hour urine collection of cortisol
    4. Dexamethasone suppression test.

Pheochromocytoma

- When to suspect a pheochromocytoma?
    1. Triad of episodic headache, diaphoresis and tachycardia ±hypertension
    2. Family history of pheo, VHL or MEN2 syndrome
    3. Clinical features of MEN2, von Hippel-Lindau disease, or pheochromocytoma/paraganglioma syndrome
    4. Known associated germ-line mutation in patient or family
    5. An undefined adrenal tumor
    6. Hypertension unexplained and/or poorly responsive to standard treatment
    7. Significant hypertension and tachycarida in response to general anesthesia, surgery or specific drugs
    8. **Note: 50% are caused by an underlying diagnosable genetic anomaly!**
- **Diagnosis**:
    1. Measurement of catecholamine metabolites (metanephrines) – urine/blood
    2. Localization by CT imaging and MRI
    3. Scintigraphy with radiolabeled metaiodobenzylguanidine (131/123IMIBG)
- **Management**:
    1. Control of blood pressure (pre-and perioperative)
    2. Surgical removal
- **Prognosis**: Risk for malignant pheo –12-47%

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