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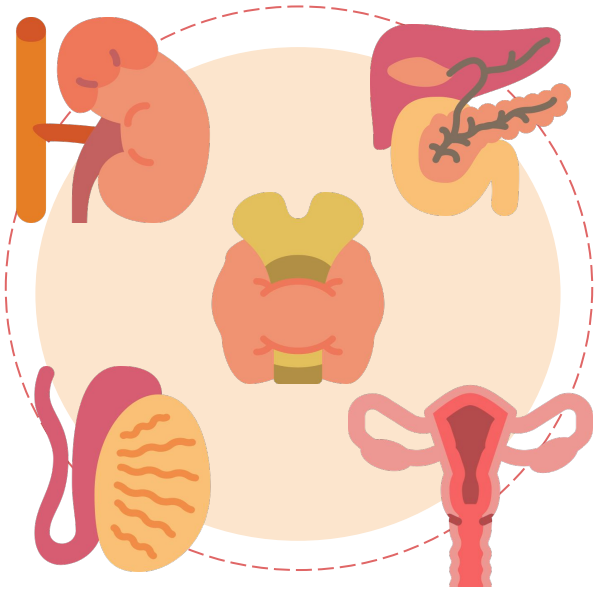

Glucocorticoids & Androgens

Objectives:

- Explain regulation of glucocorticoid and adrenal androgen secretion.
- List the trigger(s) for cortisol secretion.
- Outline the actions of glucocorticoids.
- Summarize the actions of adrenal androgens.
- Describe the causes and major manifestations of hyperadrenocorticism and hypoadrenocorticism.

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Colour index:
- Important
- ;)
- Extra

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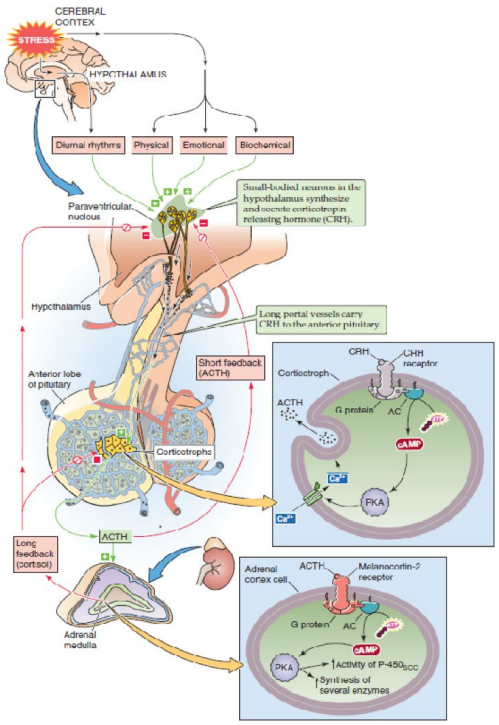
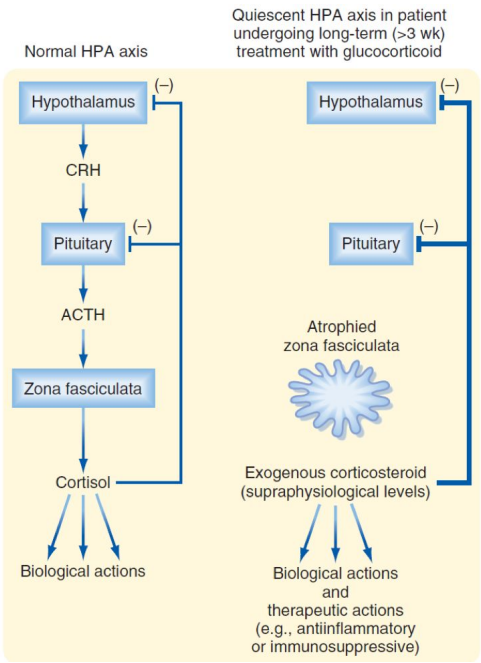
Glucocorticoids

- **Produced by** the fasciculata and reticularis layers of the adrenal cortex
- Glucocorticoids (cortisol): recognized early to increase plasma glucose levels:
  - Mobilization of amino acids from proteins
  - Enhance liver gluconeogenesis
- **Target tissues:** most body tissues
- **CRH** from hypothalamus is the major regulator of ACTH secretion
- **ADH** is also a potent ACTH secretagogue
- **ACTH** from anterior pituitary stimulates cortisol synthesis and secretion
- CRH (and ACTH) are secreted in pulses
- The greatest ACTH secretory activity occurs in the early morning hours and diminish late in the afternoon

HPA Axis

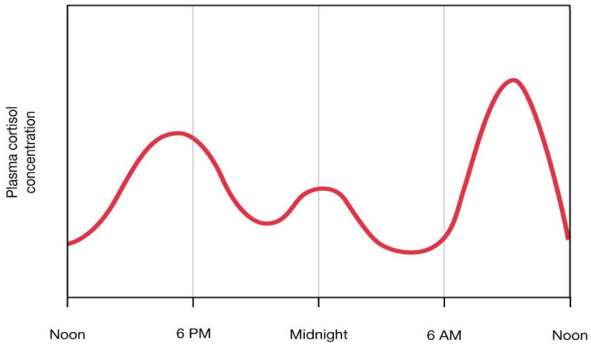


Quiescent HPA axis: Long-term GC treatment



Circadian rhythm of cortisol secretion

ACTH secretion occurs in the same rhythm



Actions of Glucocorticoids important

- Cortisol acts primarily through the **glucocorticoid receptor**
- which regulates gene transcription

Metabolic response to fasting:

- Gluconeogenesis from amino acids (increased expression of the enzymes) **(PEPCK).**
- Cortisol also decreases GLUT4-mediated glucose uptake in skeletal muscle and adipose tissue.
- Mobilization of stored fat (activation of HSL) and its use in β-oxidation and the production of ketone bodies.

Effect of glucocorticoids: on carbohydrate metabolism(anabolism)

MCQ: cortisol increases glycogen stores in which of the following?
1-liver ✓
2-muscles ✗

- Increase glycogen storage in liver cells.
- Decreased glucose utilization by the cells similar to GH..
- Promote glucose sparing by potentiating the effects of catecholamines on lipolysis, thereby making FFAs available as energy sources.
- Mobilization of amino acids from extrahepatal tissues (muscles) for gluconeogenesis.

Effect of glucocorticoids: on protein metabolism(catabolism)

- Mobilization of amino acids from non-hepatic tissues.
- Proteocatabolic effect in all body cells except of the liver.
- Decreased protein synthesis.
- Decreased amino acids transport into extrahepatic tissues (muscles, lymphatic tissues).
- Proteoanabolic effect in the liver.
- Enhanced liver proteins.
- Increased plasma proteins.

Amino acids are essential for the liver to produce:
- plasma proteins
- enzymes
-gluconeogenesis

Anti-inflammatory Effects of GC

Glucocorticoids are used to alleviate inflammation

- Stabilize lysosomal membranes (reduce their rupture and release of proteolytic enzymes).
- Inhibit production of prostaglandins, leukotrienes, and thromboxane (mediate inflammation). This occurs via inhibiting phospholipase A2.
- Decrease permeability of capillary membranes, reducing swelling.
- They also reduce the effects of histamine.
- Attenuates fever mainly because cortisol reduces release of interleukin-1 from white blood cells.
- Suppress immune system specifically T-cells;reducing cell mediated immunity

Cont.

Suppression of Immune System

- Decrease production of eosinophils and lymphocytes.
- Administration of large doses of cortisol causes significant atrophy of lymphoid tissue throughout the body.
- Decrease immunity could be fatal in diseases such as tuberculosis.
- Decrease immunity effect of cortisol is useful during transplant operations in reducing organ rejection.
- Cortisol increases the production of red blood cells.

Glucocorticoids and Stress (anti-stress hormone)

- Without GCs, the body cannot cope with even mild stressors.
- Fat & glucose metabolism.
- Maintenance of the vascular response to norepinephrine.
- Effects on CNS.

Functions of Glucocorticoids

CNS Responses

- Negative feedback control on release of ACTH
- Modulates perception & emotion
- Increase awake time

Mineral Metabolism

- Anti-vitamin D effect, reduces osteoblast differentiation

GIT

- Increases HCl secretion

Developmental

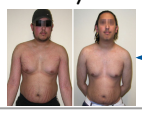
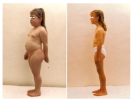
- Permissive regulation of fetal organ maturation, required for the development of CNS, retina, skin, GI tract, and lungs.
- Surfactant synthesis (phospholipid that maintains alveolar surface tension).
- Inhibition of linear growth in children due to direct effects on bone & connective tissue.

Circulation

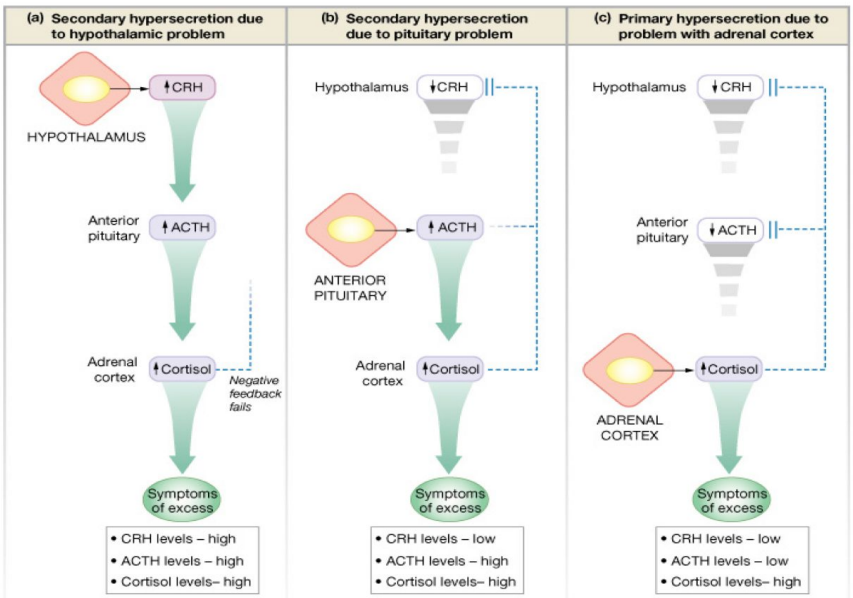
- Maintains body fluid volumes & vascular integrity.
- Cortisol levels vary with water intake.
- Cortisol has mineralocorticoid effect, Not as potent as aldosterone.
- BP regulation & cardiovascular function:
  Sensitizes arterioles to action of norepinephrine (Permissive effect)
- Decreased capillary permeability.
- Cortisol stimulates **erythropoietin** synthesis and hence increases red blood cell production.

By increasing noradrenaline receptors.

Abnormalities of Glucocorticoids

	Cushing's Syndrome	Adrenocortical insufficiency
Causes	• Cushing's syndrome results from continued high glucocorticoid levels. • 3rd - 6th decade, 4 to 1 females. **Causes**: • Pharmacologic • Pituitary adenoma 75-90% (↑ACTH) • Adrenal adenoma, carcinoma • Ectopic ACTH	**Primary causes**, ie. **Addison's disease** • autoimmune disease, tumors, infection, hemorrhage, metabolic failure, ketoconazole **Secondary causes** • Hypopituitarism, suppression by exogenous steroids *Non-functioning fasciculata and glomerularis **(e.g: Addison)** leading to deficiency of both cortisol and aldosterone.
Signs and Symptoms	• Fat is deposited in the body trunk (central obesity) causes stretching of the skin • Buffalo hump • Moon facies (subcutaneous fat in cheeks and submandibular) • Purple striae (due to to loss of collagen fibers thus thinning of the skin & fat deposition will occur) • Blood-glucose levels rises chronically, causing adrenal diabetes (insulin resistance) • ↓ Protein → severe muscle weakness & osteoporosis • May cause beta cells to die  *Purple striae*	• Fatigability, weakness, anorexia, nausea, weight loss, hypotension, hyperpigmentation, women loss of axillary and pubic hair • Loss of Na+ → Low blood pressure • Can lead to severe volume depletion and shock • ↓ cortisol results in poor blood glucose regulation (hypoglycemia) • Patient cannot cope with stress • Adrenal crisis: asthenia, severe pains in the abdomen, vascular collapse....
Treat-ment	Treatment based on cause 	Glucocorticoid replacement, mineralocorticoid replacement

Primary and Secondary Hypersecretion of Cortisol



Doctor's notes

- The doctor asked this question; how to differentiate bw ACTH dependent and ACTH independent cushing's syndrome? In the dependent ACTH will be very high while in independent ACTH will be low
- Thinning of the skin with deposition of fat or stretching of skin will lead to striae.
- increased distribution of fat leads to high levels of fat in the blood (dyslipidemia)
- Decreased lymphocyte count increases the susceptibility of the individual to infection.
- Increased RBC count lead to facial erythema.
- Increase in the mineralocorticoids function leads to hypertension and hypokalemia.
- Increased ACTH release leads to increased release of androgens, leading to acne and hirsutism.
- Causes of hyperpigmentation:
  - 1- ACTH stimulates melanocytes to produce more melanin.
  - 2- ACTH stimulates the release of melatonin stimulating hormone.
- Non-functioning fasciculata and glomerularis leading to deficiency of both cortisol and aldosterone.
- Exogenous intake of steroids is the most common cause of cushing.

Androgens

Zona reticularis:

Produces significant amounts of androgens, mostly dehydroepiandrosterone sulfate (DHEAS).

Hormonal Control: ACTH

Target tissue: General body cells

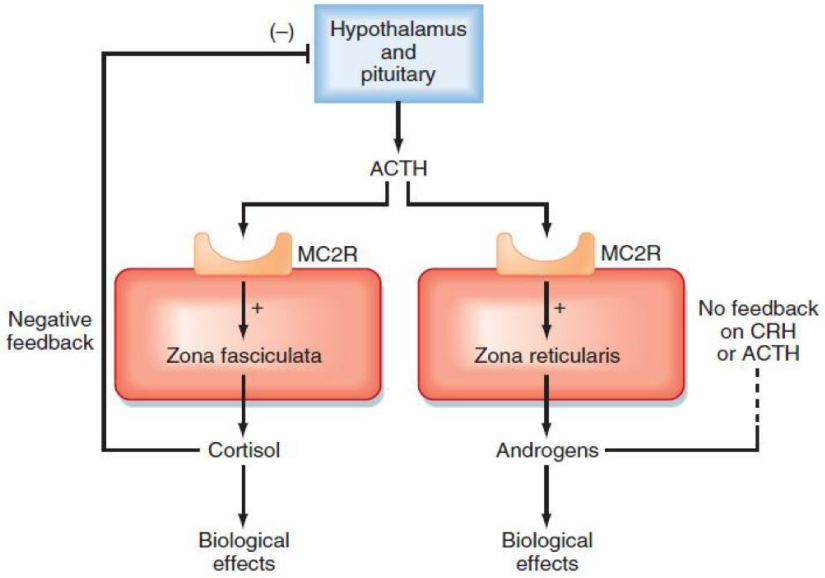
Androgens:

- Androgens are the hormones that exert masculinizing effects.
- They promote anabolism and growth.
- Adrenal androgens have little androgenic activity, but they provide a pool of circulating precursor for peripheral conversion to more potent androgens (e.g. testosterone, T) and estrogens, (e.g. estradiol).
- The adrenal cortex produces both androgens “male sex hormones” and estrogens or “female sex hormones”.
- The adrenal cortex in both sexes produces small amounts of sex hormone of the opposite sex. Additional small amounts of sex hormones come from non adrenal sources. Some testosterone in males is converted into estrogen by the enzyme **aromatase** found in adipose tissues.
- In females, ovaries produce androgen as an intermediate step in estrogen production. Little of this androgen is released in the blood instead of being converted into estrogen.
- About 90% of adrenal androgens are bound to albumin and 3% approximately is bound to sex hormone-binding globulin **(SHBG).**
- **DHEAS** has high affinity to albumin, half-life 7-10 hours. **DHEA** low affinity, 15-30 min.
- DHEA, DHEAS, and Androstenedione are converted to the potent androgens T and DHT in peripheral tissues.

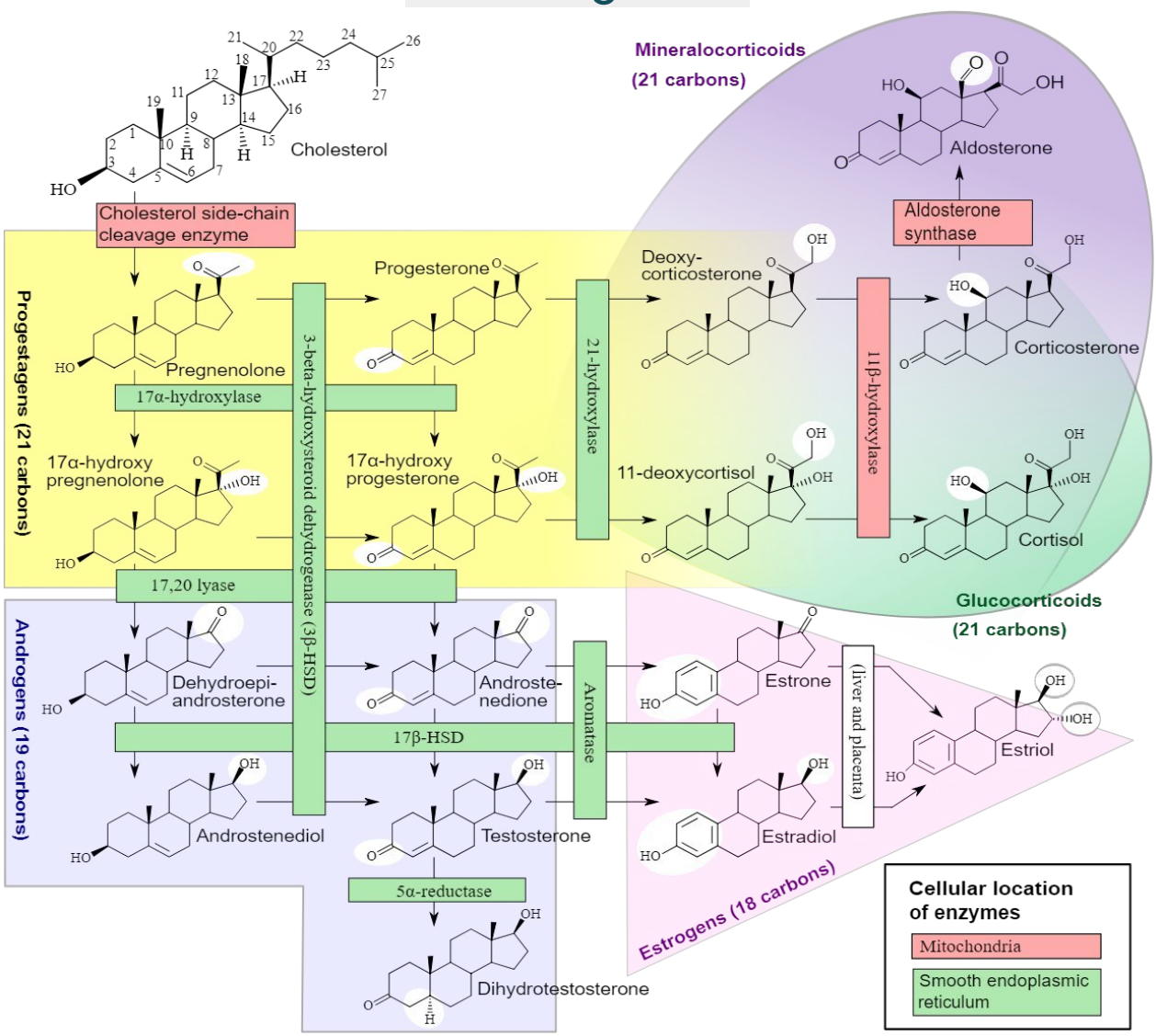
A subset of androgens, adrenal androgens, include:

- Dehydroepiandrosterone (DHEA)
- DHEA sulfate (DHEAS)
- Androstenedione
- Androstenediol
- 11β-hydroxyandrostenedione (11OHA)
- 11β-hydroxytestosterone (11OHT)

The "loophole" in the hypothalamic-pituitary-adrenal axis



Steroidogenesis



Adrenal cortex

Male sex hormones (Androgens)

- Adrenal androgens includes :
  - dehydroepiandrosterone (DHEA)
  - Androstenedione.

Female sex hormones

- Estrogens
- Progesterone

*The adrenal cortex in both sexes produces small amounts of sex hormone of the opposite sex.

Adrenal Androgens

DHEA

- It is the most abundant adrenal androgen
- DHEA is the primary precursor of natural estrogens.
- Normally they exert very little masculinizing effect (weak) when secreted in normal amount (mild effect in female).

Androstenedione

- An androgenic steroid produced by the testes, adrenal cortex, and ovaries
- Androstenediones are converted metabolically to testosterone and to estrogens in the fat and other peripheral tissues.
- It is an important source of estrogen in men and postmenopausal Women.
- Androstenedione were used as an athletic or body building supplement.

Role of Androgens:

IN MALES

- Spermatogenesis
- Inhibition of fat deposition
- Muscle mass
- Brain: Androgen levels have been implicated in the regulation of human aggression and libido.
- masculinization of the developing male fetus (including penis and scrotum formation).

IN FEMALES

- growth of pubic and axillary hair.
- pubertal growth spurt development
- Androgens have potential roles in relaxation of the myometrium preventing premature uterine contractions in pregnancy
- development and maintenance of female sex drive (libido).

Adrenogenital Syndrome

Excessive adrenal androgens secretion

Causes

1. Adrenocortical tumors
2. Congenital adrenal hyperplasia
   - Inherited as autosomal recessive diseases.
   - Affect both boys and girls.
   - Due to deficiency of one of the enzymes of the cortisol synthesis (21-hydroxylase) and steroids are 'diverted' to becoming androgens.
   - Lead to increase ACTH leading to excessive production of adrenal androgens.

Diagnosis

- It is often difficult to make a diagnosis.
- However, the excretion of **17-ketosteroids** (derived from androgens) in urine may be 10 to 15 times more than normal, used in diagnosing the disease.

Treatment

- GC replacement

Before birth

Pseudohermaphroditism:

- Before 12 week in female fetus.
- XX true female with external male genitalia

Cause?

- Expose of the mother to excessive androgens.

After birth

- ➢ Virilization
- ➢ Development of male characters:
  - Increase bulk of muscles
  - Hoarseness
  - Increase body & facial hair
  - Atrophy of the breast
  - Amenorrhea

In prepubertal male

- Precocious puberty
- Early appearance of male characters
- Increase musculature
- Development of external genitalia organ to adult size
- No spermatogenesis

In the adult male

The virilizing characteristics of adrenogenital syndrome are usually obscured by the normal virilizing characteristics of the testosterone secreted by the testes.

Congenital Adrenal Hyperplasia (CAH):

What is it?

- It is a familial disorder of adrenal steroid biosynthesis with autosomal recessive mode of inheritance.
- The defect is expressed as adrenal enzyme deficiency.

Enzymes deficiencies

- Most important enzyme deficiencies:

1. **21 α-Hydroxylase** (>80% of cases).
2. **11 β-Hydroxylase** (5-10% of cases)
3. **17 α-Hydroxylase**

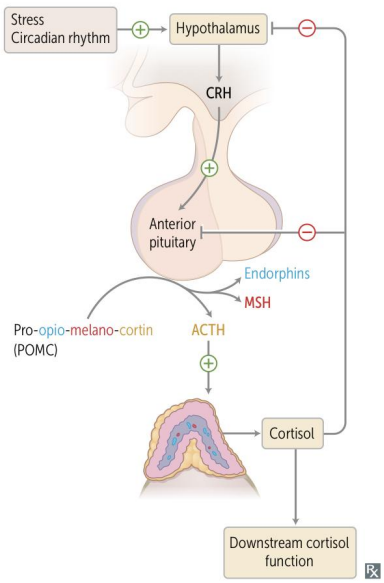
Clinical significance

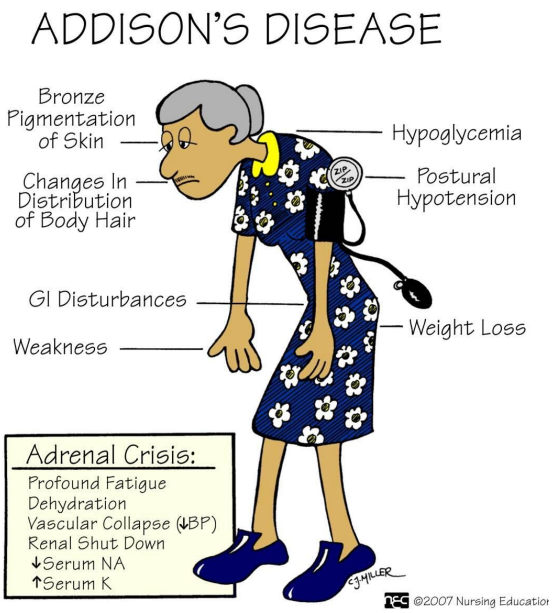
1. The enzyme deficiency (21-hydroxylase) causes reduction in end-products, accumulation of hormone precursors & increased ACTH production. (↓ cortisol and aldosterone & ↑ ACTH)
2. The clinical picture reflects the effects of inadequate production of cortisol & aldosterone and the increased production of androgens & steroid metabolites.

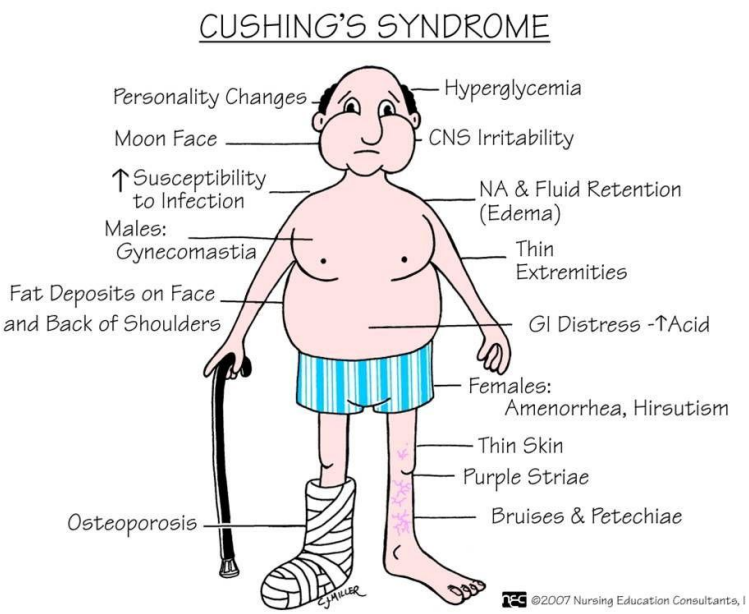
Deficiency of 21-hydroxylase enzyme will lead to the accumulation of 17-hydroxyprogesterone and a shift to the androgen synthesis pathway leading to an increase in androgens.

Summary

Cortisol

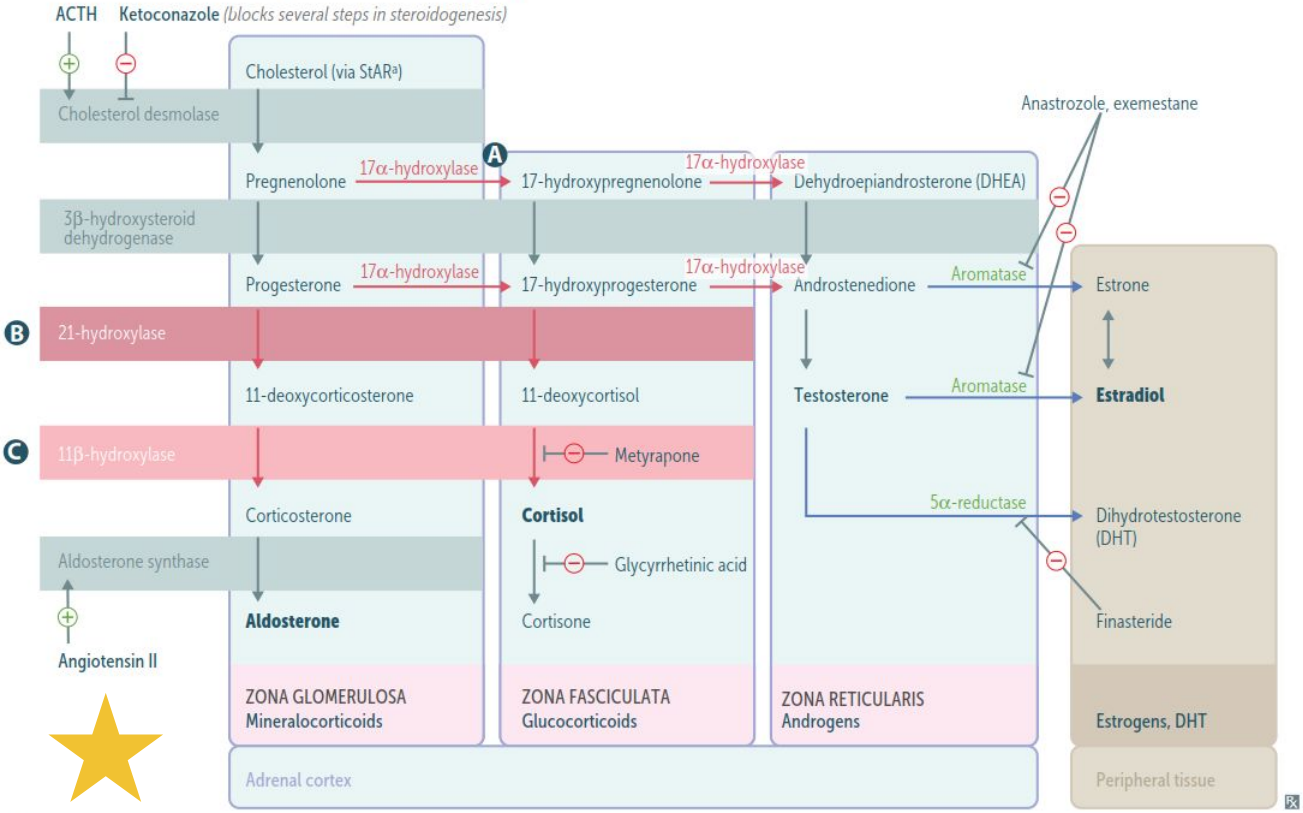
SOURCE	Adrenal zona fasciculata.	Bound to corticosteroid-binding globulin.
FUNCTION	↑ **A**ppetite ↑ **B**lood pressure: ▪ Upregulates α_1-receptors on arterioles → ↑ sensitivity to norepinephrine and epinephrine (permissive action) ▪ At high concentrations, can bind to mineralocorticoid (aldosterone) receptors ↑ **I**nsulin resistance (diabetogenic) ↑ **G**luconeogenesis, lipolysis, and proteolysis (↓ glucose utilization) ↓ **F**ibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae) ↓ **I**nflammatory and **I**mmune responses: ▪ Inhibits production of leukotrienes and prostaglandins ▪ Inhibits WBC adhesion → neutrophilia ▪ Blocks histamine release from mast cells ▪ Eosinopenia, lymphopenia ▪ Blocks IL-2 production ↓ **B**one formation (↓ osteoblast activity)	Cortisol is a **A BIG FIB**. Exogenous corticosteroids can cause reactivation of TB and candidiasis (blocks IL-2 production). 
REGULATION	CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion.	Chronic stress induces prolonged secretion.





Summary

Adrenal steroids and congenital adrenal hyperplasias



[a]Rate-limiting step.

ENZYME DEFICIENCY	MINERALOCORTICOIDS	CORTISOL	SEX HORMONES	BP	[K+]	LABS	PRESENTATION
A 17α-hydroxylase[a]	↑	↓	↓	↑	↓	↓ androstenedione	XY: ambiguous genitalia, undescended testes XX: lacks 2° sexual development
B 21-hydroxylase[a] Most common deficiency	↓	↓	↑	↓	↑	↑ renin activity ↑ 17-hydroxy-progesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
C 11β-hydroxylase[a]	↓ aldosterone ↑ 11-deoxycorti-costerone (results in ↑ BP)	↓	↑	↑	↓	↓ renin activity	XX: virilization

[a]All congenital adrenal enzyme deficiencies are characterized by skin hyperpigmentation (due to ↑ MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to ↑ ACTH stimulation).
If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

MCQs

Q1/ Cortisol and GH are most dissimilar in their metabolic effects on which of the following?

A. Protein synthesis in muscle
B. Glucose uptake in peripheral tissues
C. Plasma glucose conc
D. Mobilization of glucose

Q2/ A 59-year old woman has osteoporosis, hypertension, hirsutism, and hyperpigmentation. MRI indicates that the pituitary gland is not enlarged. Which condition is most consistent with these findings?

A. Pituitary ACTH-secreting tumor
B. Ectopic ACTH-secreting tumor
C. Adrenal adenoma
D. Addison's disease

Q3/ High dose steroid exerts anti-inflammatory action by:

A. Stabilize lysosomal membrane
B. Inhibits histamine release
C. Inhibits fibroblastic action
D. All of the above

Q4/ Cortisone is administered to a 30-year-old woman forthe treatment of an autoimmune disease. Which ofthe following is most likely to occur?

A. Increased ACTH secretion
B. Increased insulin secretion
C. Increased muscle mass
D. Hypoglycemia between meals

Q5/ Pregnenolone is not in the biosynthetic pathway of which substance?

A. Cortisol
B. Estrogen
C. DHEA
D. 1,25(OH)2D

Q6/ Cortisol can increase the the count of which of the following:

A. RBCs
B. WBCs
C. T lymphocytes
D. B lymphocytes

Q7/ The Primary precursor of natural estrogen is:

A. DHEA
B. Corticosterone
C. Cortisol
D. Androstenedione

Q8/ Which of the following would be associated with parallel changes in aldosterone and cortisol secretion?

A. Addison's disease
B. Cushing's disease
C. Cushing's syndrome (adrenal tumor)
D. A low-sodium diet

Q9/Which option would not be efficacious in the treatment of patients with type 2 diabetes?

A. Weight loss
B. Insulin injections
C. thiazolidinediones
D. Glucocorticoids

Answers
1.A 2.B 3.D 4.B 5.D 6.A 7.A 8.A 9.D