Adrenal gland Physiology

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Learning outcomes

- Hormones secreted by adrenal gland
- Adrenal cortex hormones - Synthesis,metabolism,regulation,actions
- Adrenal medullary hormones-

  Synthesis,metabolism,regulation,actions

Adrenal gland

- The human adrenal glands, each weighing only ~4 g, are located above the upper pole of each kidney in the retroperitoneal space.

- They produce four principal hormones: cortisol, aldosterone, epinephrine (adrenaline), and norepinephrine

- Each adrenal gland is composed of an inner medulla and an outer cortex

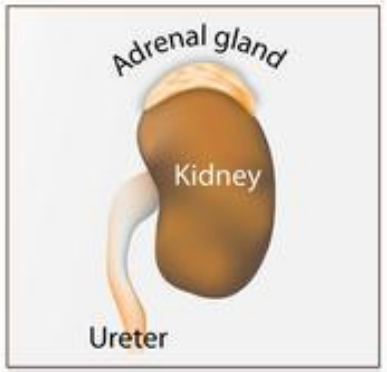
Adrenal gland-Hormones

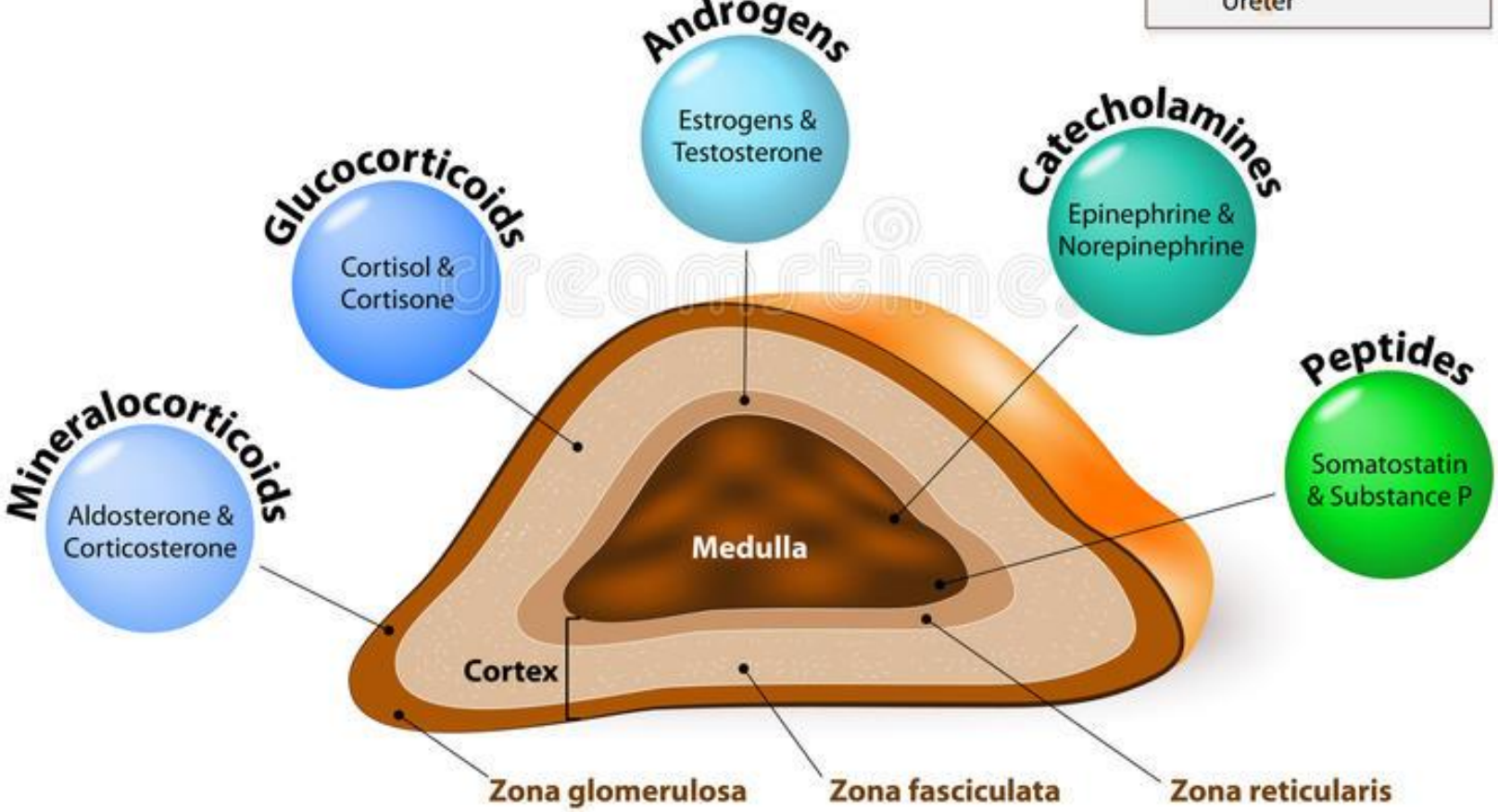
- The cortex produces two principal steroid hormones
- cortisol
- aldosterone
- several androgenic steroids-DHEA

- The medulla produces
- epinephrine
- norepinephrine

ADRENAL GLAND

(hormones)



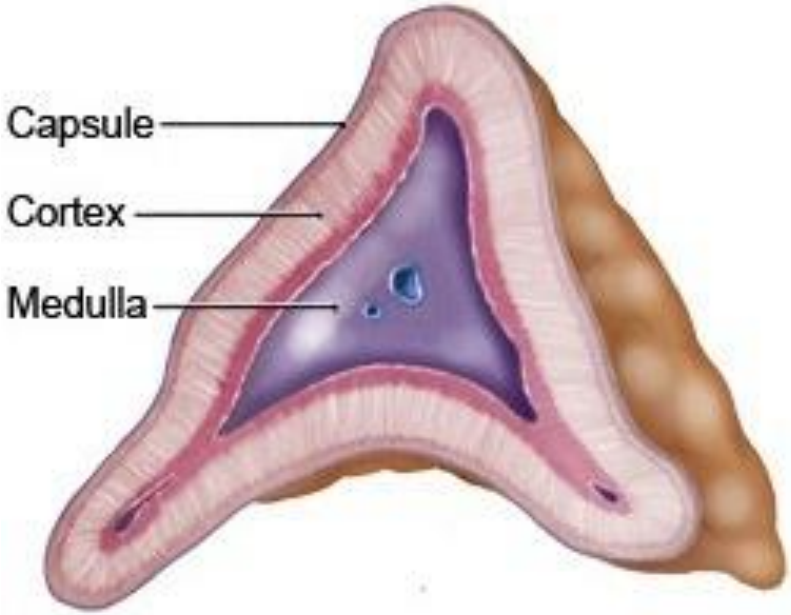


Adrenal cortex

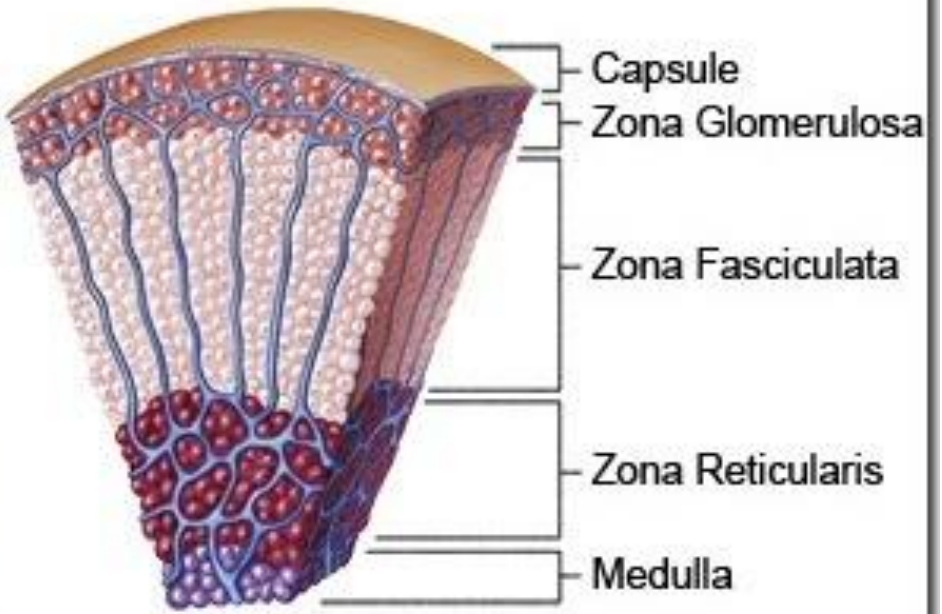
- Divided into three cellular layers:
- Glomerulosa layer near the surface
- Fasciculata layer in the midcortex
- Reticularis layer near the cortical-medullary junction.

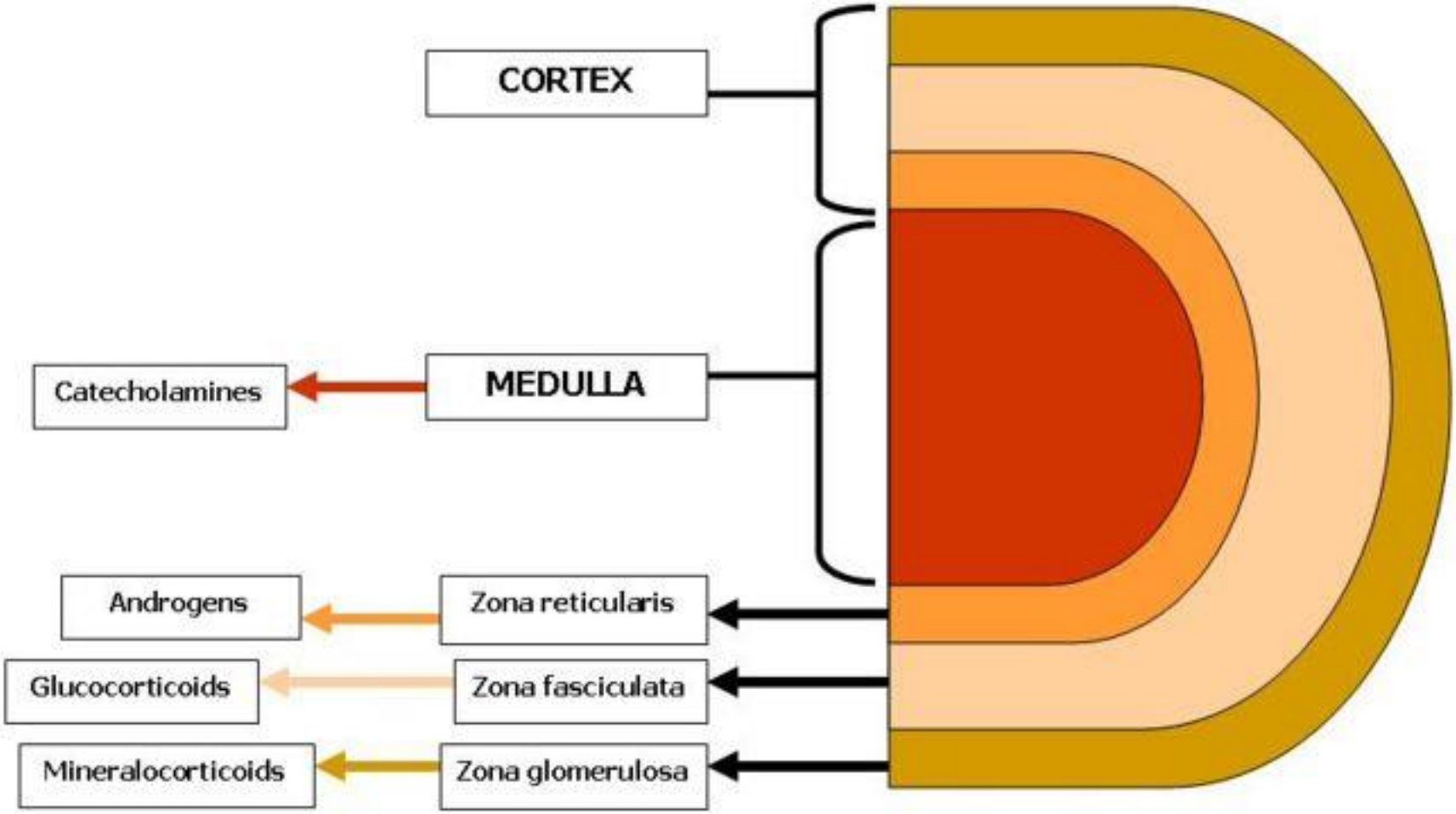
Adrenal Gland Cross Sections

Transverse Section



Microscopic Section




CORTEX
MEDULLA
Catecholamines
Androgens
Zona reticularis
Glucocorticoids
Zona fasciculata
Mineralocorticoids
Zona glomerulosa

Adrenal cortex-Hormones

- Aldosterone, the main mineralocorticoid in humans, is made in the glomerulosa cell layer
- Cortisol, the principal glucocorticoid, is made in the fasciculata and to a small extent in the reticularis layer
- The adrenal androgens—dehydroepiandrosterone (DHEA) and its sulfated form DHEAS—are made in the reticularis layer

The Adrenal Cortex: Cortisol

- Steroid hormones are divided into three major classes based on their actions:

- glucocorticoids
- mineralocorticoids
- sex steroids

- Cortisol is the primary glucocorticoid hormone in humans

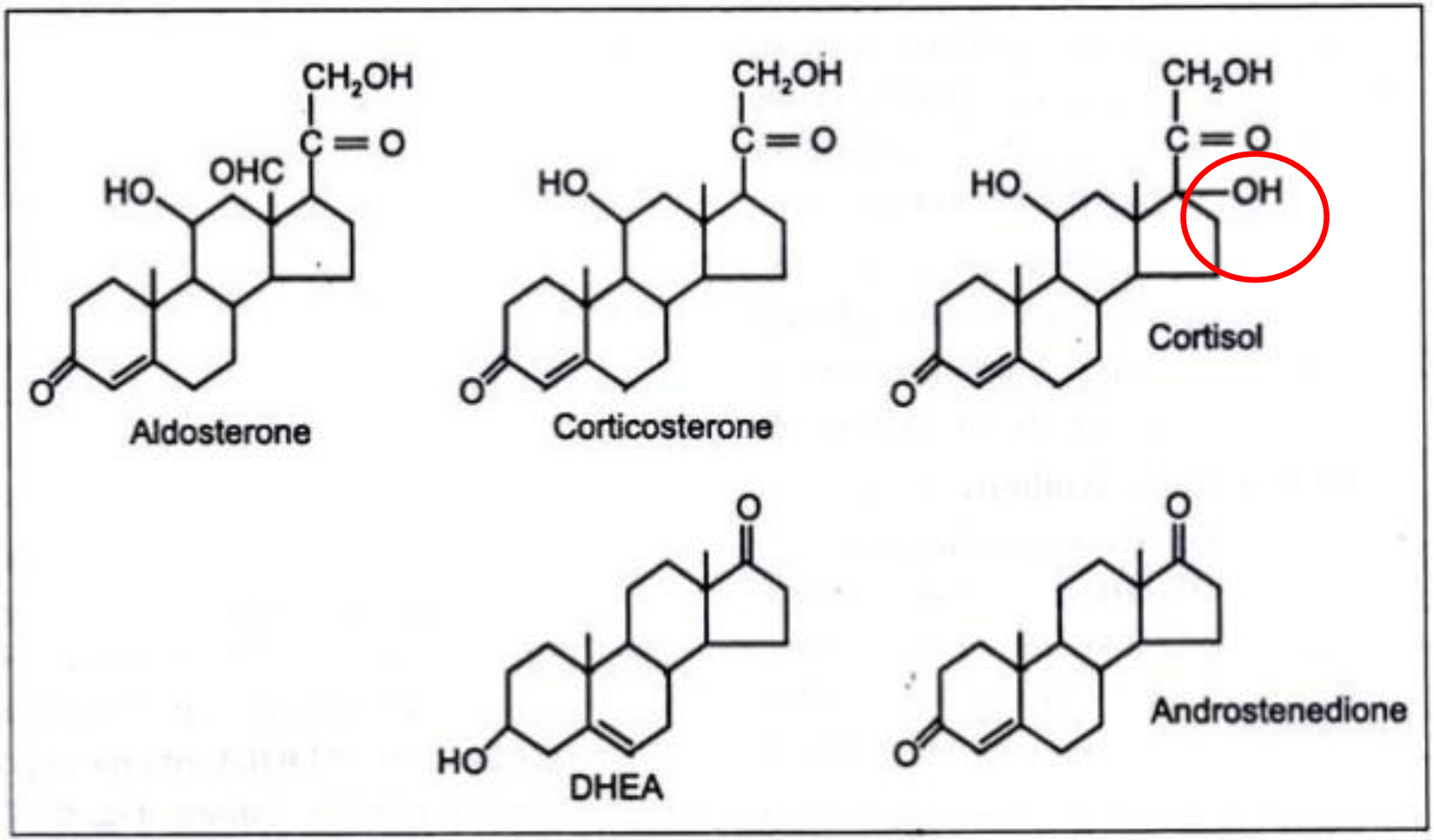
- Cortisol is the prototypical naturally occurring glucocorticoid

Cortisol

- The structures of cortisol and aldosterone differ only slightly:

- Aldosterone lacks the –OH group at position 17 and has an aldehyde (aldo) group at position 18.

- Despite the seemingly minor chemical difference, aldosterone at physiological concentrations has virtually no glucocorticoid activity.


CH2OH
C=O
HO
OHC
O
Aldosterone
CH2OH
C=O
HO
O
Corticosterone
CH2OH
C=O
HO
OH
O
Cortisol
O
HO
DHEA
O
O
Androstenedione

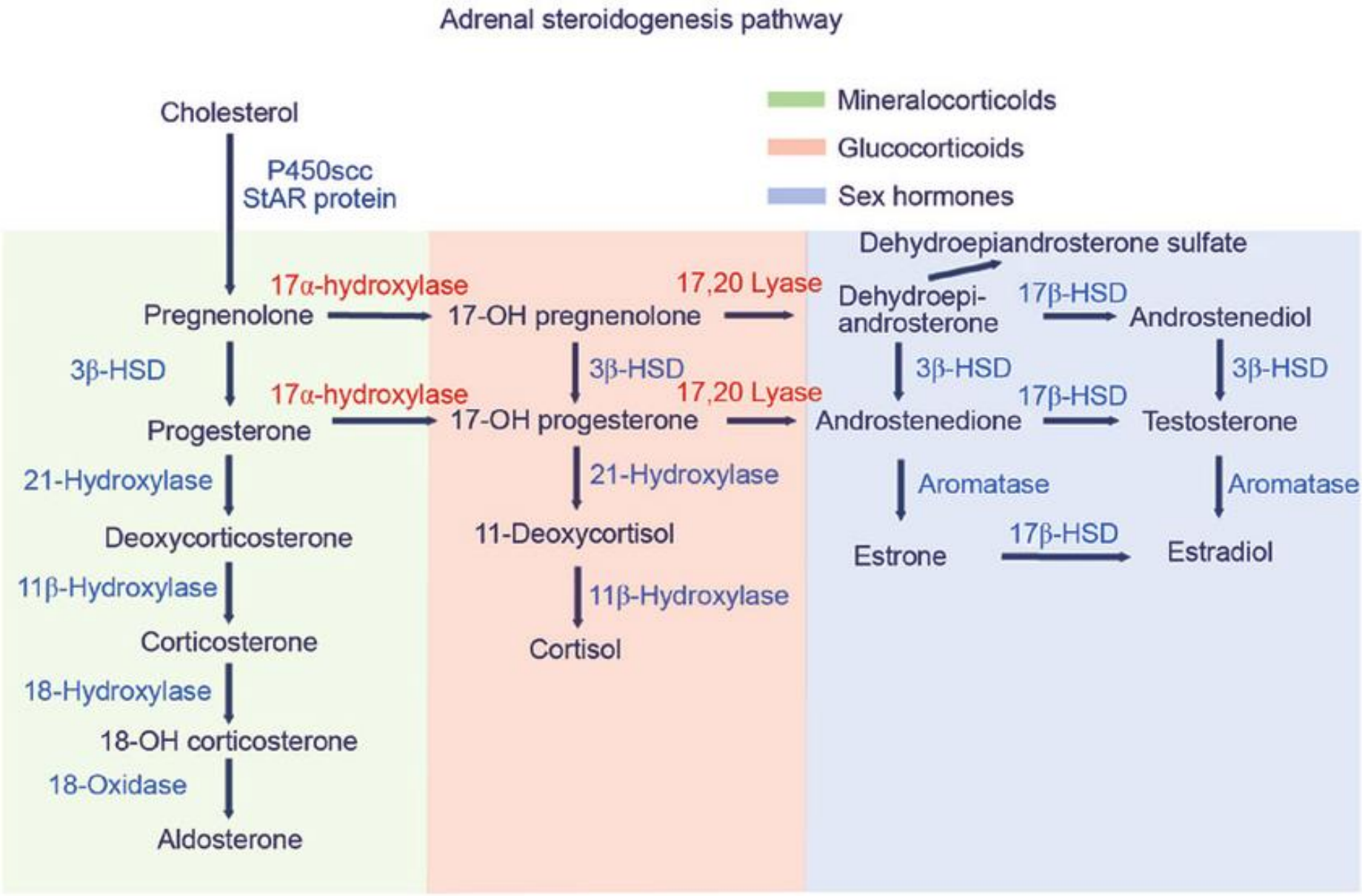
Synthesis of cortisol

- The adrenal zona fasciculata converts cholesterol to cortisol
- Synthesis of cortisol, as for all steroid hormones, starts with cholesterol .
- Like other cells producing steroid hormones, the adrenal gland has two sources of cholesterol
- (1) import cholesterol from circulating cholesterol-containing low-density lipoprotein (LDL)
- (2) Synthesize cholesterol de novo from acetate

Synthesis of cortisol

- Cholesterol is metabolized through a series of five reactions to make either cortisol or aldosterone

- All relevant enzymes are located in either the mitochondria or smooth endoplasmic reticulum (SER), and except for 3β-hydroxysteroid dehydrogenase (3β-HSD), belong to the family of cytochrome P-450 oxidases


Adrenal steroidogenesis pathway
Mineralocorticolds
Glucocorticoids
Sex hormones
Cholesterol
P450scc
StAR protein
Pregnenolone
17α-hydroxylase
17-OH pregnenolone
17,20 Lyase
Dehydroepiandrosterone sulfate
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17β-HSD
Androstenediol
3β-HSD
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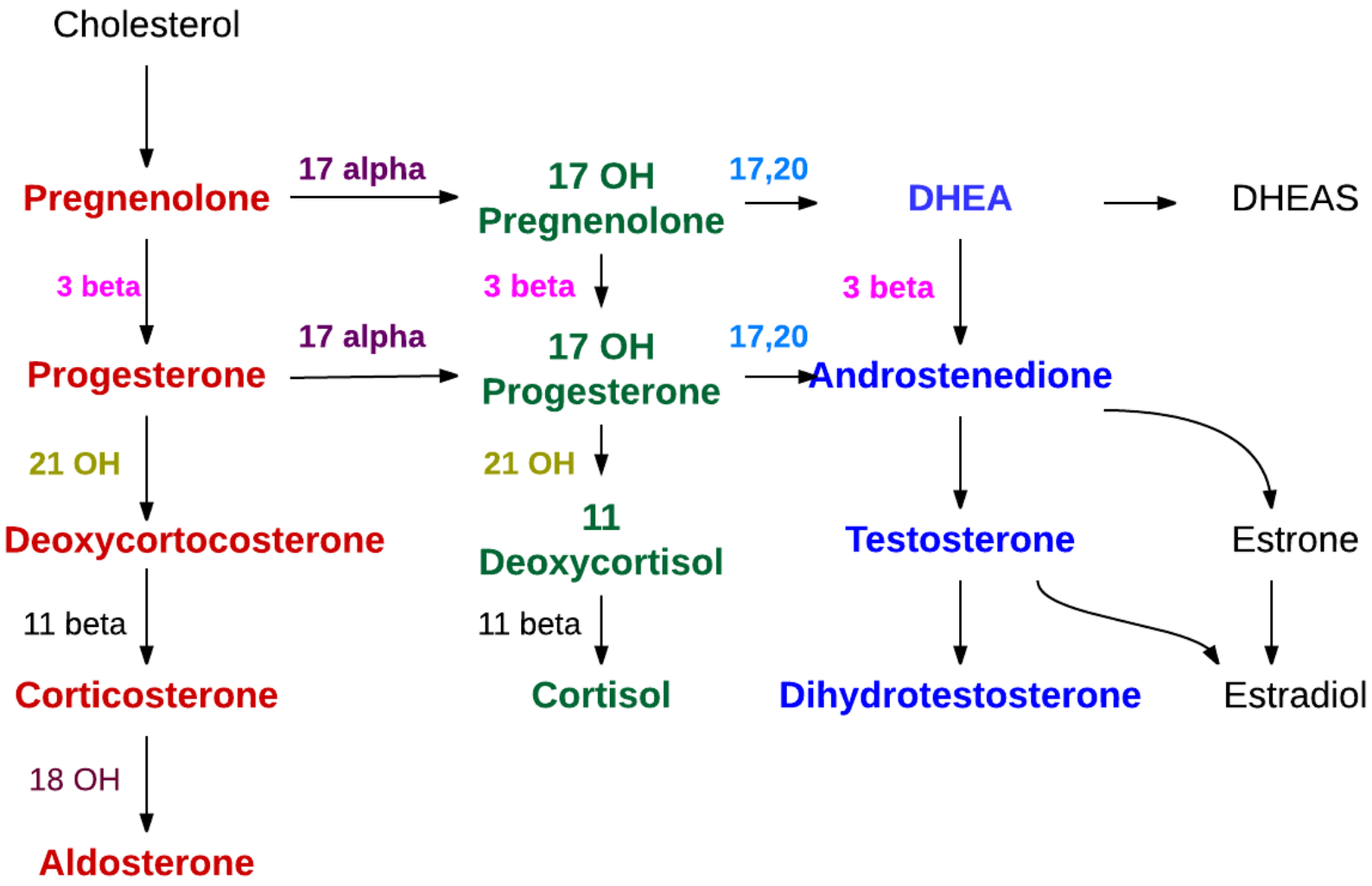
3β-HSD
Progesterone
17α-hydroxylase
17-OH progesterone
17,20 Lyase
Androstenedione
17β-HSD
Testosterone
21-Hydroxylase
21-Hydroxylase
Aromatase
Aromatase
Deoxycorticosterone
11-Deoxycortisol
Estrone
17β-HSD
Estradiol
11β-Hydroxylase
11β-Hydroxylase
Corticosterone
Cortisol
18-Hydroxylase
18-OH corticosterone
18-Oxidase
Aldosterone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DHEA
DHEAS
3 beta
3 beta
3 beta
Progesterone
17 alpha
17 OH Progesterone
17,20
Androstenedione
21 OH
21 OH
Deoxycortocosterone
11 Deoxycortisol
Testosterone
Estrone
11 beta
11 beta
Corticosterone
Cortisol
Dihydrotestosterone
Estradiol
18 OH
Aldosterone

Transport of cortisol

- The cortisol diffuses out of the cells and into the blood plasma
- 90% of the cortisol is transported bound to corticosteroid-binding globulin (CBG), also known as transcortin.
- Transcortin is a 383–amino-acid glycoprotein whose affinity for cortisol is ~30-fold higher than that for aldosterone
- An additional ~7% of the circulating cortisol is bound to albumin.
- Only 3% to 4% of the circulating cortisol is free.

Target Tissues

- Cortisol affects the principal glucose-regulatory tissues,
  - liver, fat, and muscle

- . Other sites -bone, skin, other viscera, hematopoietic and lymphoid tissue, and the central nervous system

- Although cortisol is the primary glucocorticoid in humans, in other species (e.g., the rat), corticosterone is the major glucocorticoid

Actions of cortisol

- In liver-induces the synthesis of enzymes involved in gluconeogenesis and amino-acid metabolism → gluconeogenesis → enhancing hepatic glucose production.

- In muscle stimulates the breakdown of muscle protein, which releases amino acids for uptake by the liver.

- Promotes lipolysis in adipose tissue. The fatty acids thus released provide an alternative fuel to glucose

- Although fat is mobilized from the extremities, some is also deposited centrally

Cortisol main effect is to increase concentration of blood glucose at the expense of fat and proteins.

CHO metabolism

- 1) ↑ Gluconeogenesis
- 2) Decrease utilization of glucose by cells everywhere else in the body except the brain

- cortisol has caused a diabetogenic effect or increases blood glucose

Cortisol effects with respect to Protein metabolism

- 1) Cortisol stimulates protein degradation in all cells except liver cells

- 2) Cortisol promotes formation proteins(anabolism) by the liver which is opposite to the rest of the body proteins.

- Summary on protein metabolism: ↓ muscle proteins, ↑ liver proteins.

Cortisol on Lipid Metabolism

- Cortisol increases lipolysis or increased fatty acids in the blood from adipose tissue

Cortisol presence allows for permissiveness

- Cortisol presence permits catecholamines to induce vasoconstriction.
- If not, a person lacking cortisol, may go into circulatory shock

Anti-inflammatory Effect of cortisol

- Anti-inflammatory Synthetic glucocorticoids are being administered to inhibit all steps in inflammation that are actually very destructive, such as in rheumatoid arthritis.

- They act to decrease inflammation and swelling and stabilize capillary membranes.

- They don’t affect the underlying disease process but merely suppress the body’s response to the disease.

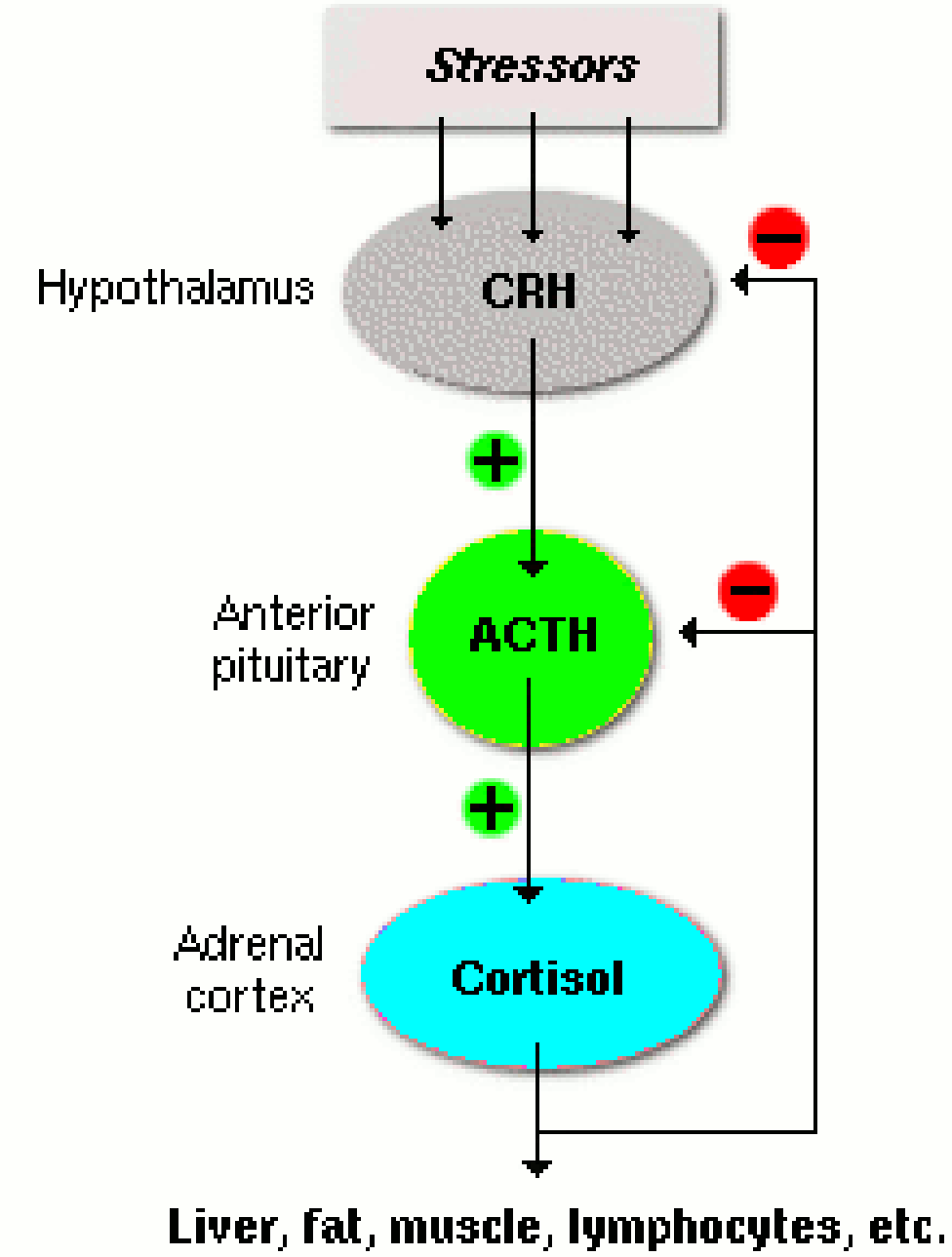
Immunosuppressive Effect of cortisol

- Immunosuppression – Inhibit the effects of the immune system by knocking out of commission the white blood cells responsible for antibody production and destruction of foreign cells

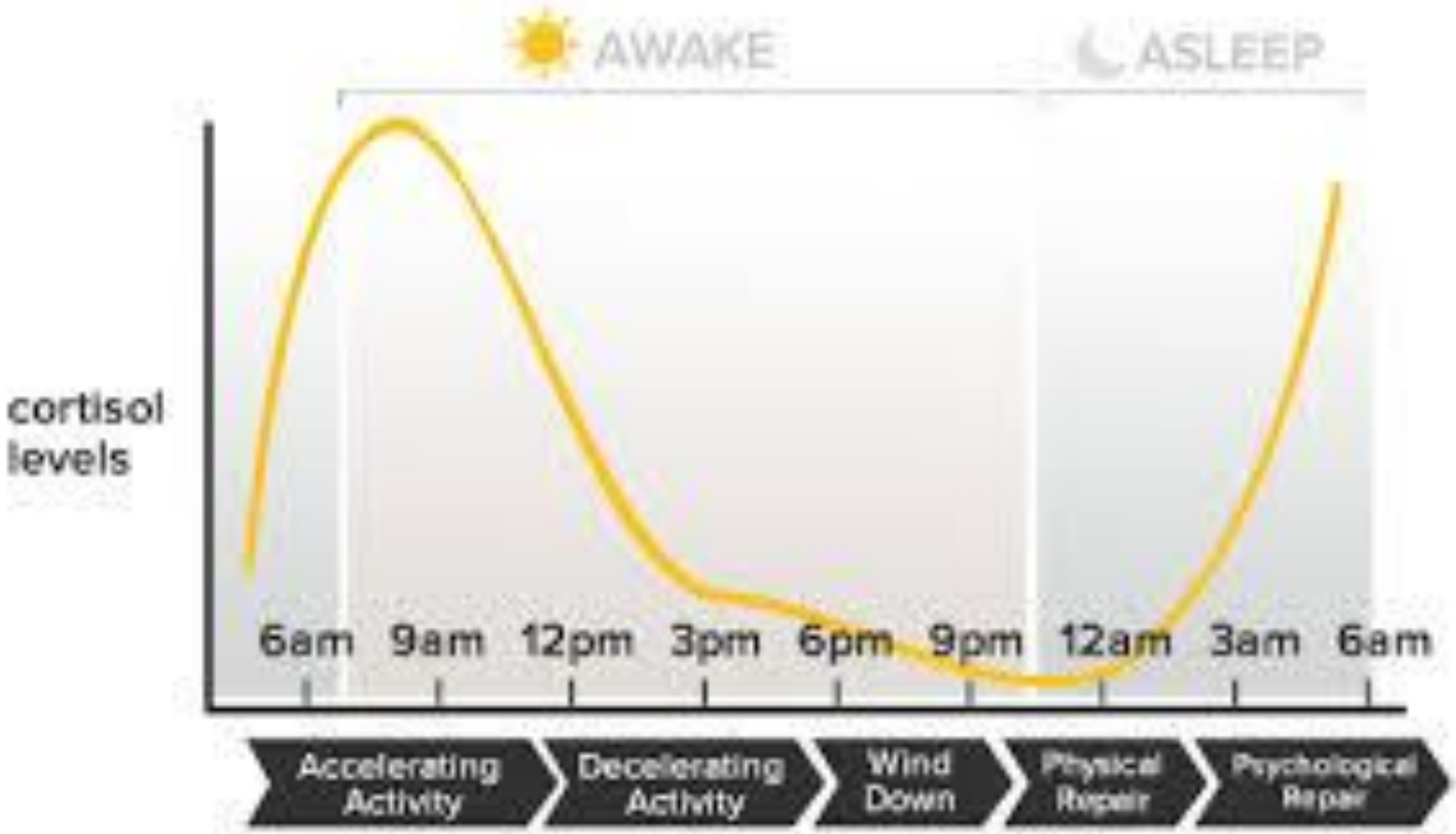
- Useful in allergic disorders and preventing organ transplant rejection.

Mechanism of action

- Cortisol binds to a cytoplasmic receptor that translocates to the nucleus and modulates transcription in multiple tissues
- Virtually all nucleated tissues in the body contain receptors for glucocorticoids.
- The glucocorticoid receptor (GR) is primarily located in the cytoplasm
- GRs are structurally similar to the receptors for mineralocorticoids, sex steroids, vitamin D, vitamin A, and thyroid hormone.

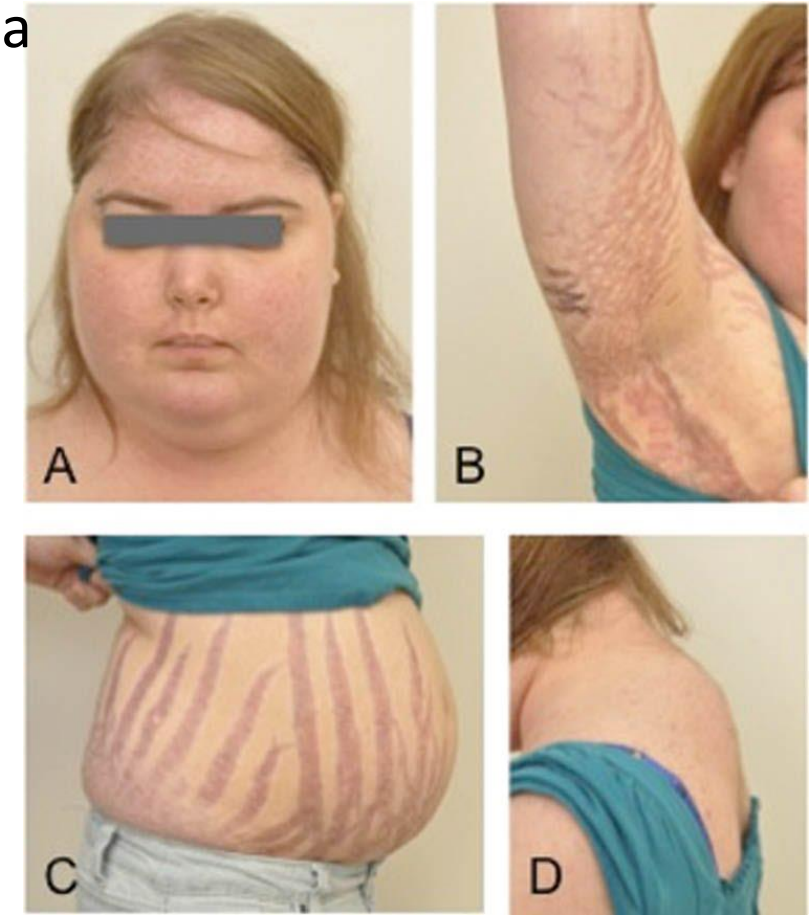

Stressors
Hypothalamus
CRH
Anterior pituitary
ACTH
Adrenal cortex
Cortisol
Liver, fat, muscle, lymphocytes, etc.

Diurnal Variation in secretion



Cushing Syndrome

- Due to prlong increase in plasma glucocorticoids
- Described by Harvey Cushing
- Can be ACTH dependent or Independent



Cushing's Syndrome

1) ACTH Dependent 80%

Pituitary adenoma (65-75%)

Ectopc ACTH (10-15%)

- Carcinoid (usually bronchial)
- Small cell lung cancer
- Pheochromocytoma (rare)

Ectopic CRH (<1%)

2) ACTH Independent 20%

Adrenal Adenoma (10%)

Adrenal Carcinoma (10%)

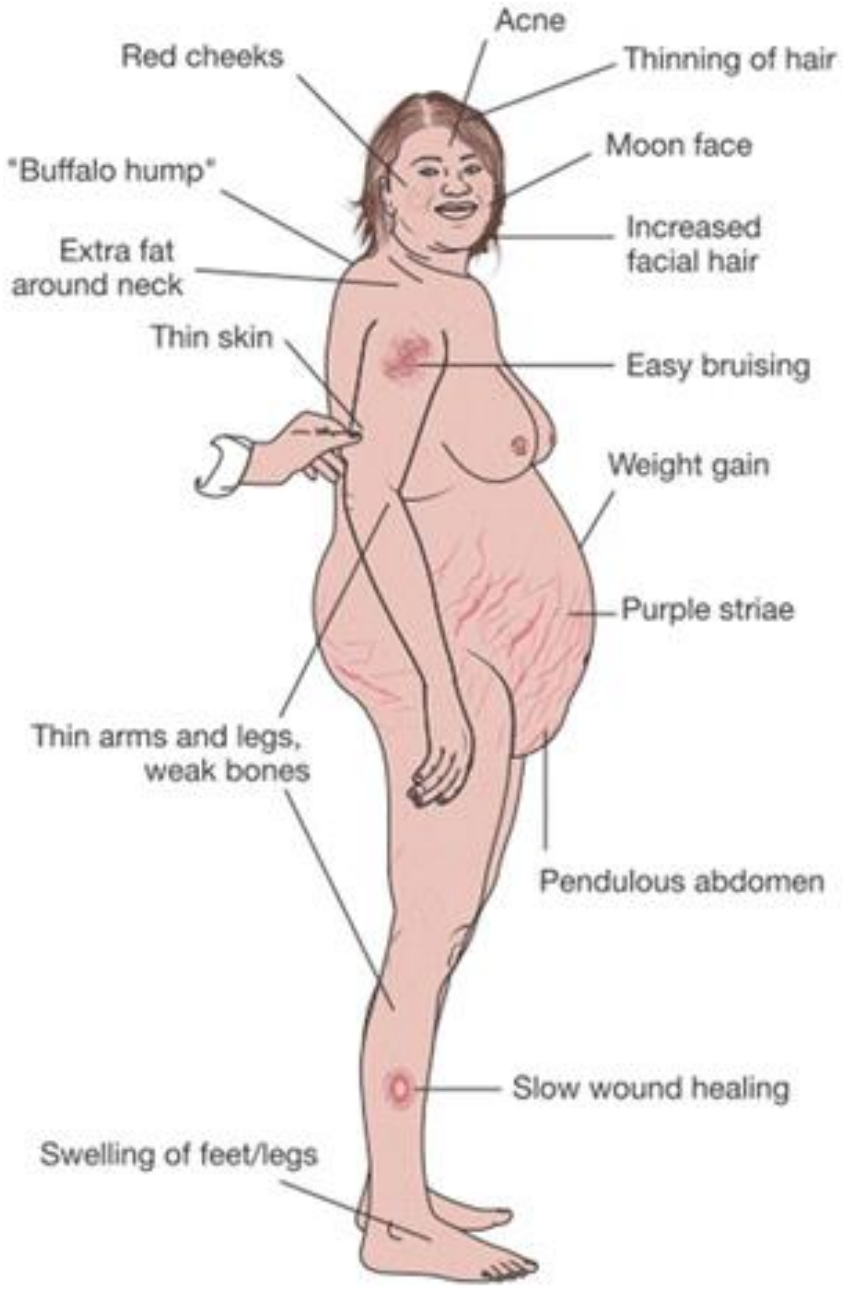
Nodular adrenal hyperplasia

- Primary pigmented
- Massive macronodular
- Food dependent (GIP mediated)

3) Pseudo-Cushing's

Exogenous Corticosteroids

- Oral
- Inhaled/Topical – hi potency
- Surreptitious



Hypertension

Poor short-term memory

Irritability

Fatigue

Poor concentration

Menstrual irregularity

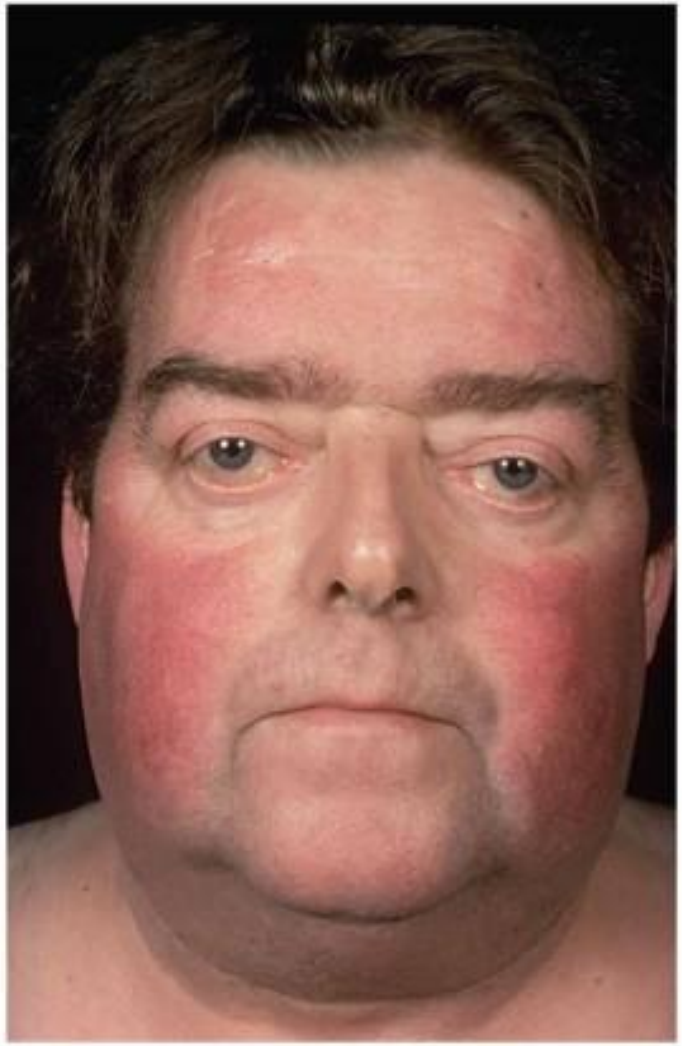
Glucose intolerance

Headaches

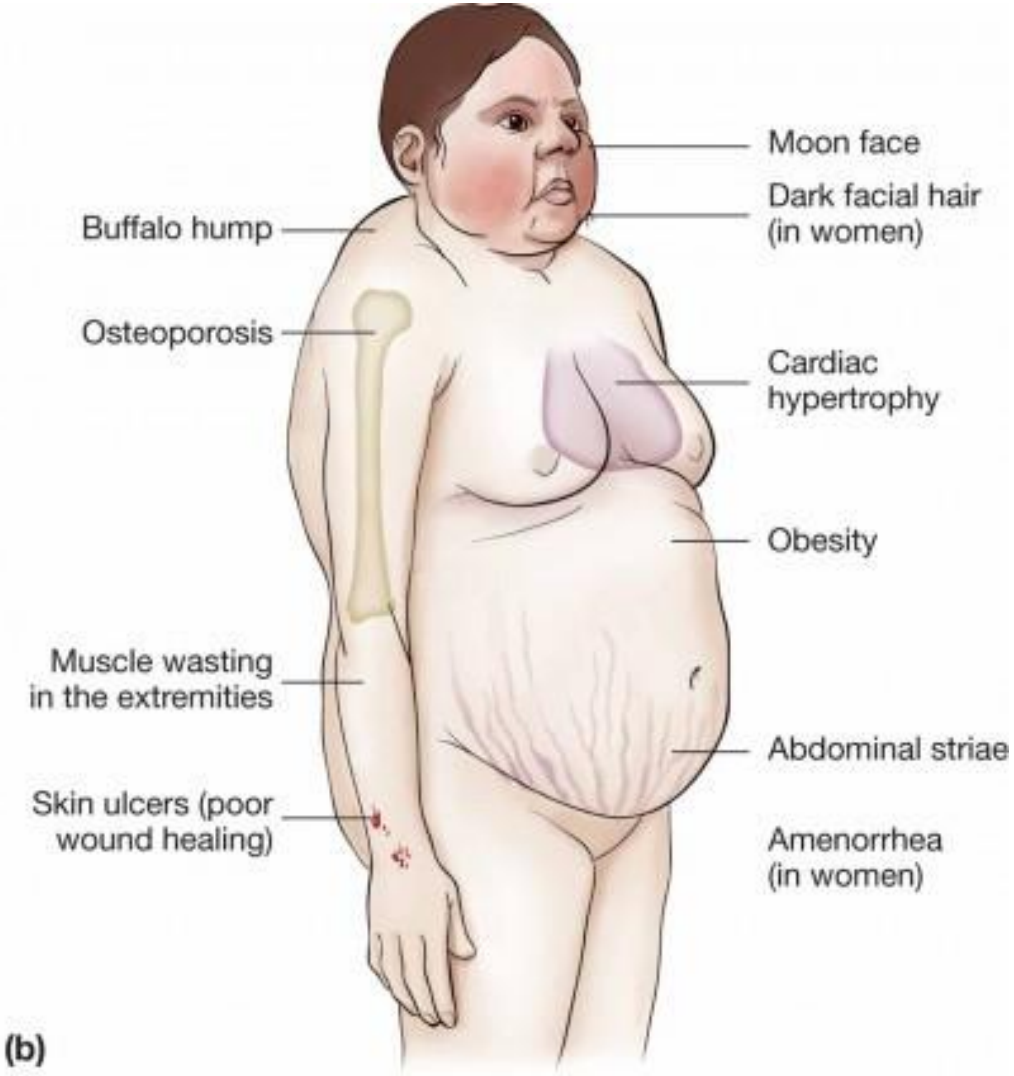
Insomnia

Recurrent infection

Depression



(a)


Moon face
Dark facial hair (in women)
Buffalo hump
Osteoporosis
Cardiac hypertrophy
Obesity
Muscle wasting in the extremities
Abdominal striae
Skin ulcers (poor wound healing)
Amenorrhea (in women)

(b)

Home work

- Explain the
- 1.Thin skin
- 2.Easy bruisibility
- Central adiposity
- High blood pressure
- High blood glucose

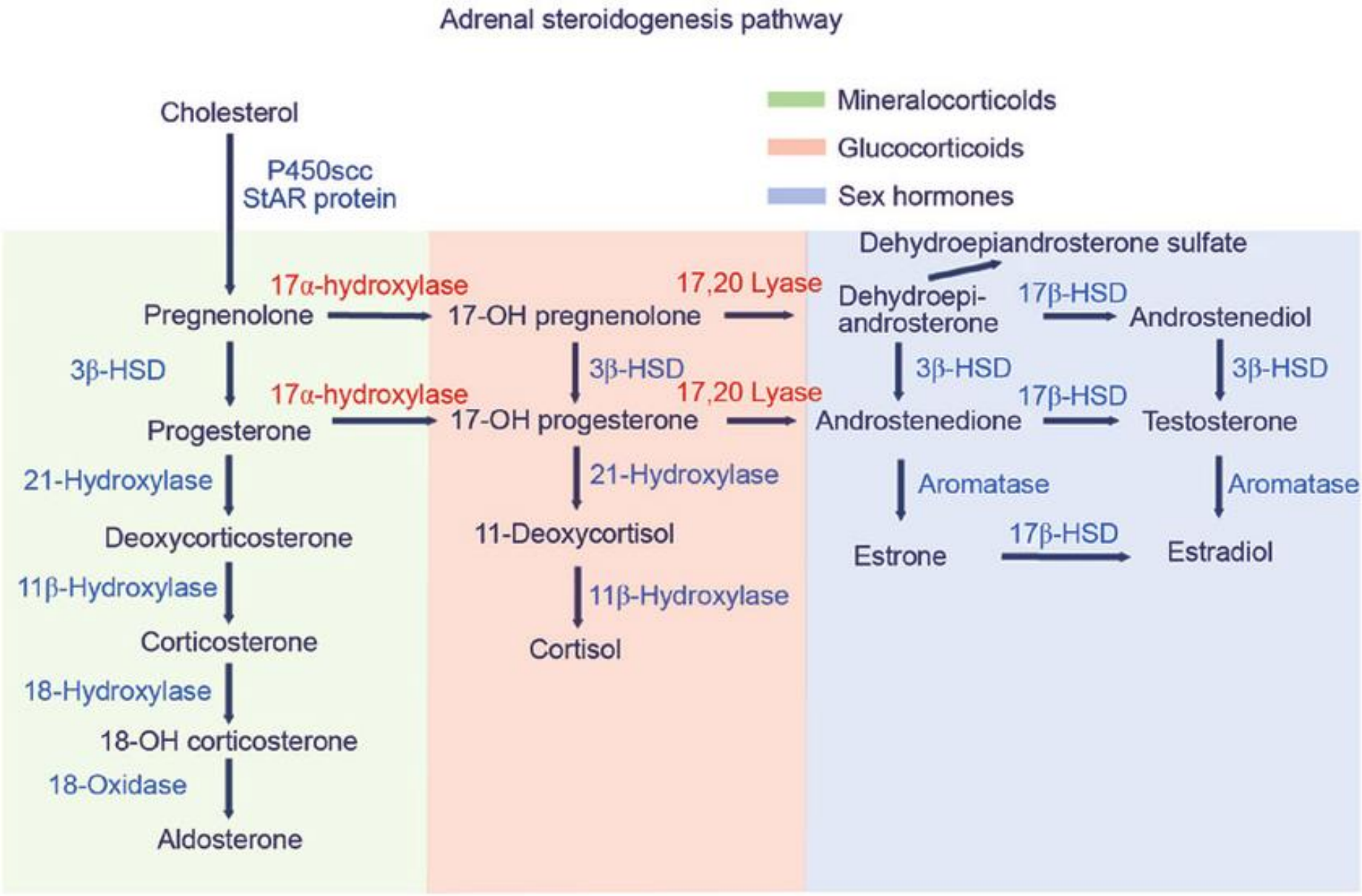
In Cushing disease

The Adrenal Cortex: Aldosterone

- The mineralocorticoid aldosterone is the primary regulator of salt balance and extracellular volume

- The glomerulosa cells of the adrenal cortex synthesize aldosterone from cholesterol via progesterone

- Adrenal cortex synthesizes aldosterone from cholesterol by using P-450 enzymes in a series of five steps.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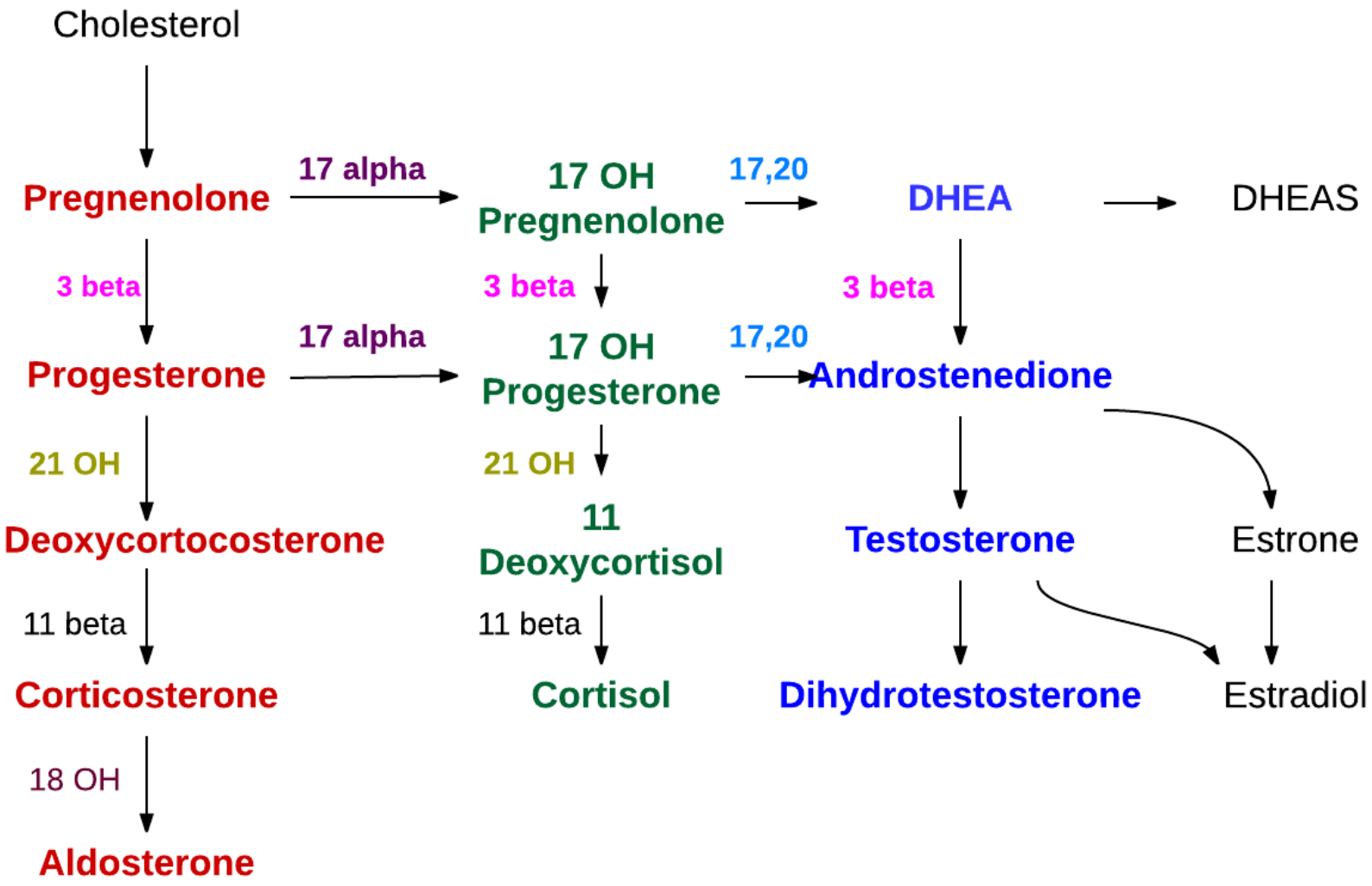
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11 Deoxycortisol
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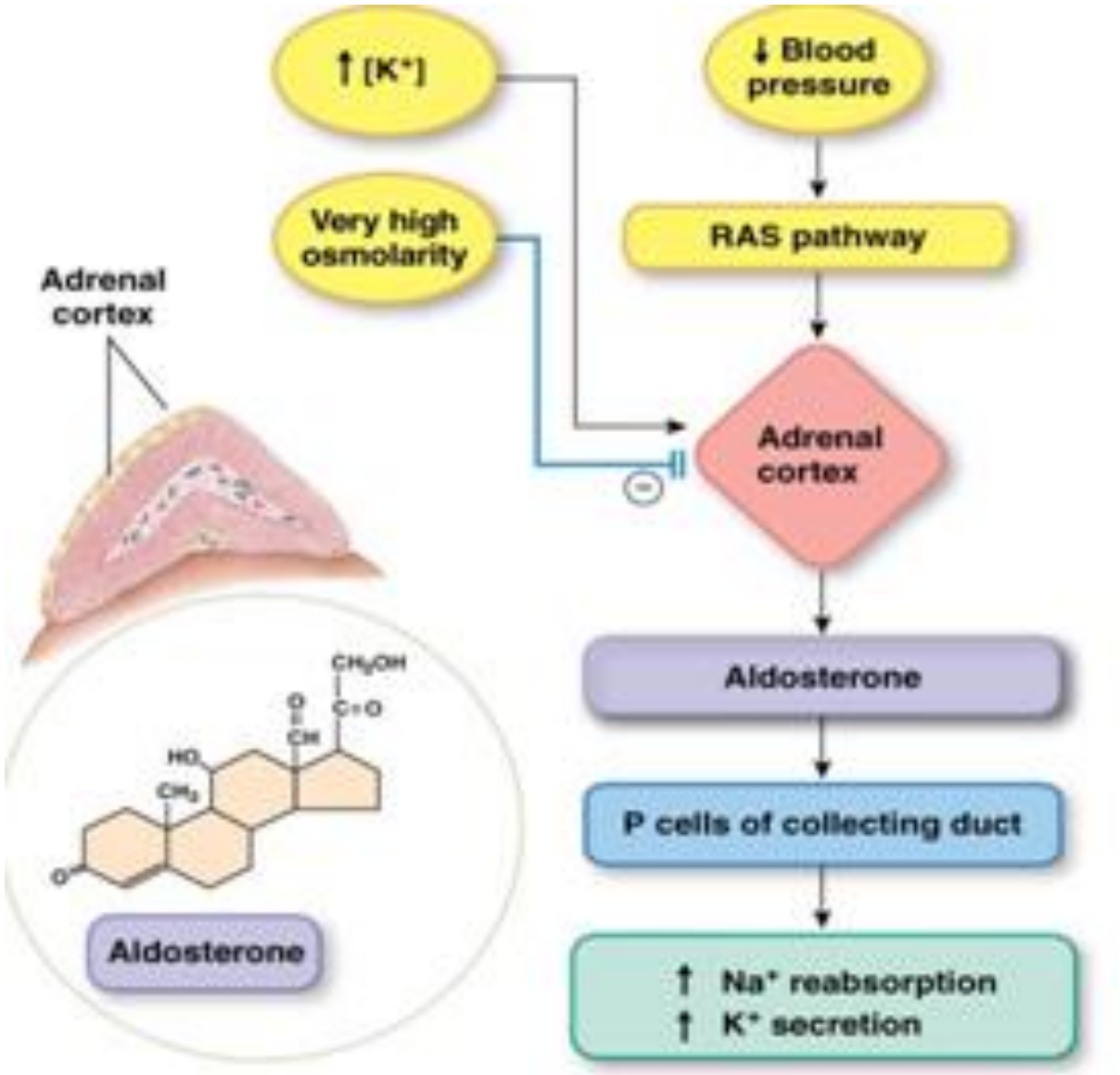
Estrone
11 beta
11 beta
Corticosterone
Cortisol
Dihydrotestosterone
Estradiol
18 OH
Aldosterone

Aldosterone

- Glomerulosa cells are the only ones that contain aldosterone synthase
- These cells are the exclusive site of aldosterone synthesis.
- Although ACTH also stimulates the production of aldosterone in the glomerulosa cell, increases in extracellular [K+] and the peptide hormone ANG II are physiologically more important secretagogues
- Once secreted, ~37% of circulating aldosterone remains free in plasma. The rest weakly binds to CBG (~21%) or albumin (~42%).


↑ [K⁺]
↓ Blood pressure
Very high osmolarity
RAS pathway
Adrenal cortex
Adrenal cortex
Aldosterone
P cells of collecting duct
↑ Na⁺ reabsorption
↑ K⁺ secretion
Aldosterone

Actions

- Aldosterone stimulates Na+ reabsorption and K+ excretion by the renal tubule

- Stimulate the kidney to reabsorb Na+ and water and enhance K+ secretion.
- Aldosterone has similar actions on salt and water transport in the colon, salivary glands, and sweat glands.

- Aldosterone, like cortisol and all the other steroid hormones, acts principally by modulating gene transcription

Actions

- Increases the activity of several key proteins involved in Na+ transport
- It increases transcription of the Na-K pump and augment distal Na+ reabsorption.
- Raises the expression of apical Na+ channels and of an Na/K/Cl cotransporter.
- The net effect of these actions is to increase Na+ reabsorption and K+ secretion.

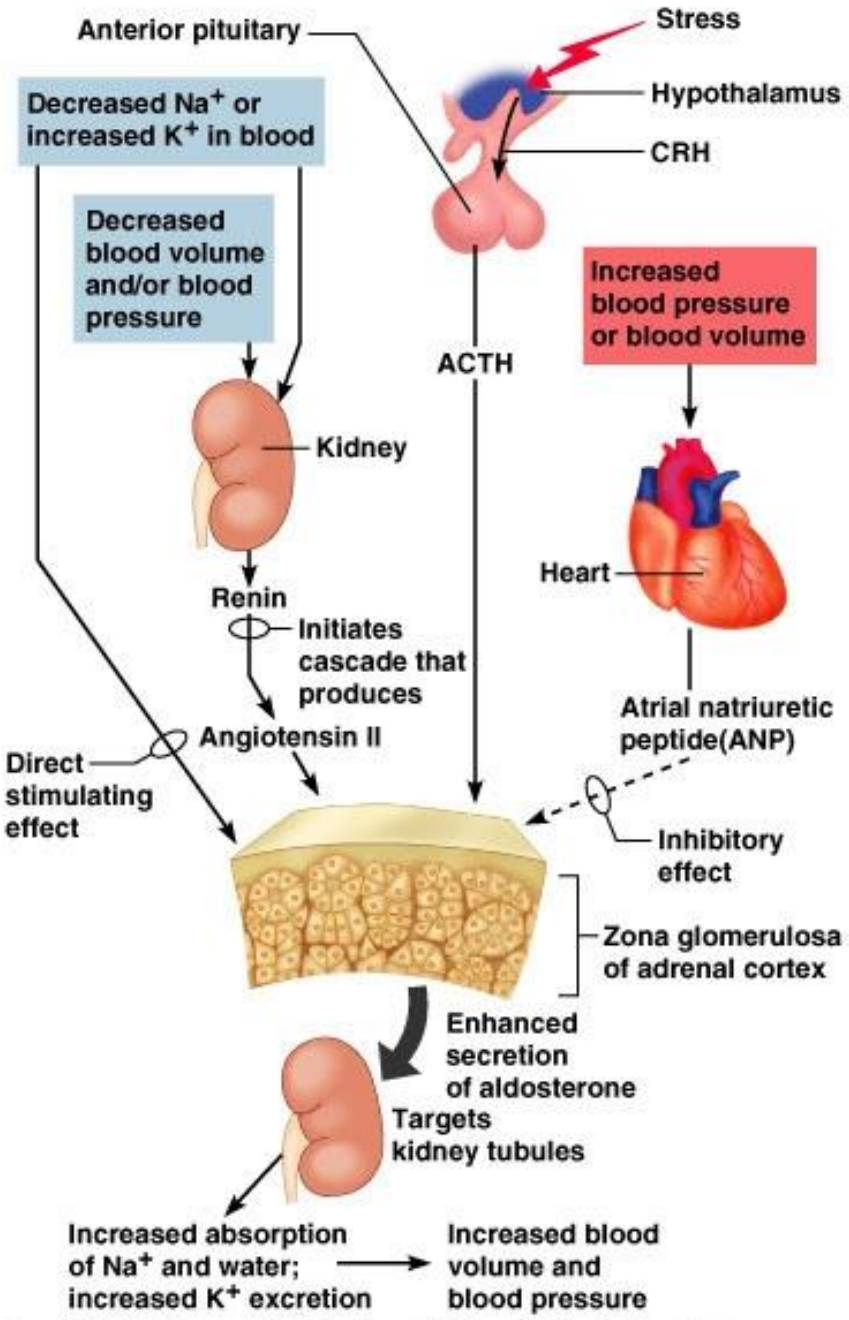
Actions

- Aldosterone regulates only that small fraction of renal Na+ reabsorption that occurs in the distal tubule and collecting duct

- Although most Na+ reabsorption occurs in the proximal tubule by aldosterone-independent mechanisms, loss of aldosterone-mediated Na+ reabsorption can result in significant electrolyte abnormalities

- Life-threatening hyperkalemia and, in the absence of other compensatory mechanisms, hypotension

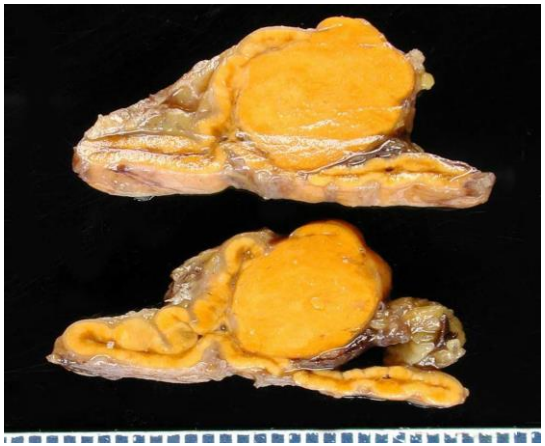
- Conversely, excess aldosterone secretion produces hypokalemia and hypertension



Primary Hyperaldosteronism

- Hyperaldosteronism is responsible for ~10% of hypertension and for an even greater fraction of treatment-resistant hypertension.

- Primary hyperaldosteronism can result from-
  - ☐ isolated adrenal adenoma
  - ☐ bilateral adrenal hyperplasia
  - ☐ adrenal carcinoma



Primary Hyperaldosteronism

- In patients with adenomas of the glomerulosa cell, the disorder is called Conn syndrome.

- Hypertension and hypokalemia frequently develop in these patients

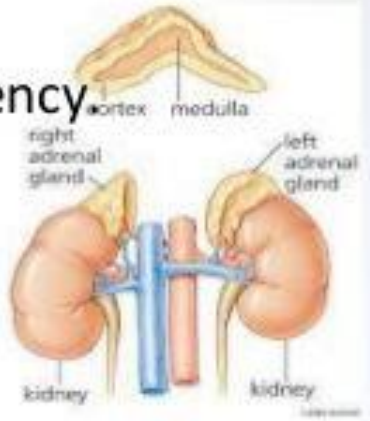
- Plasma renin concentration is characteristically suppressed in this form of hypertension.

Adrenal Insufficiency

- Occurs due to lack of glucocorticoids ± aldosterone
- Life threating condition
- Can lead to circulatory collapse

TYPES

- There are three major types of adrenal insufficiency

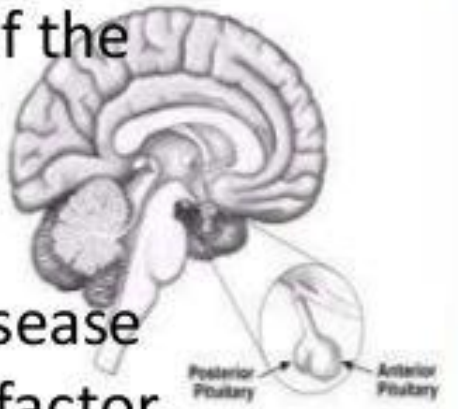


- **Primary adrenal insufficiency:**

is due to impairment of the adrenal glands.(Addison's Disease)

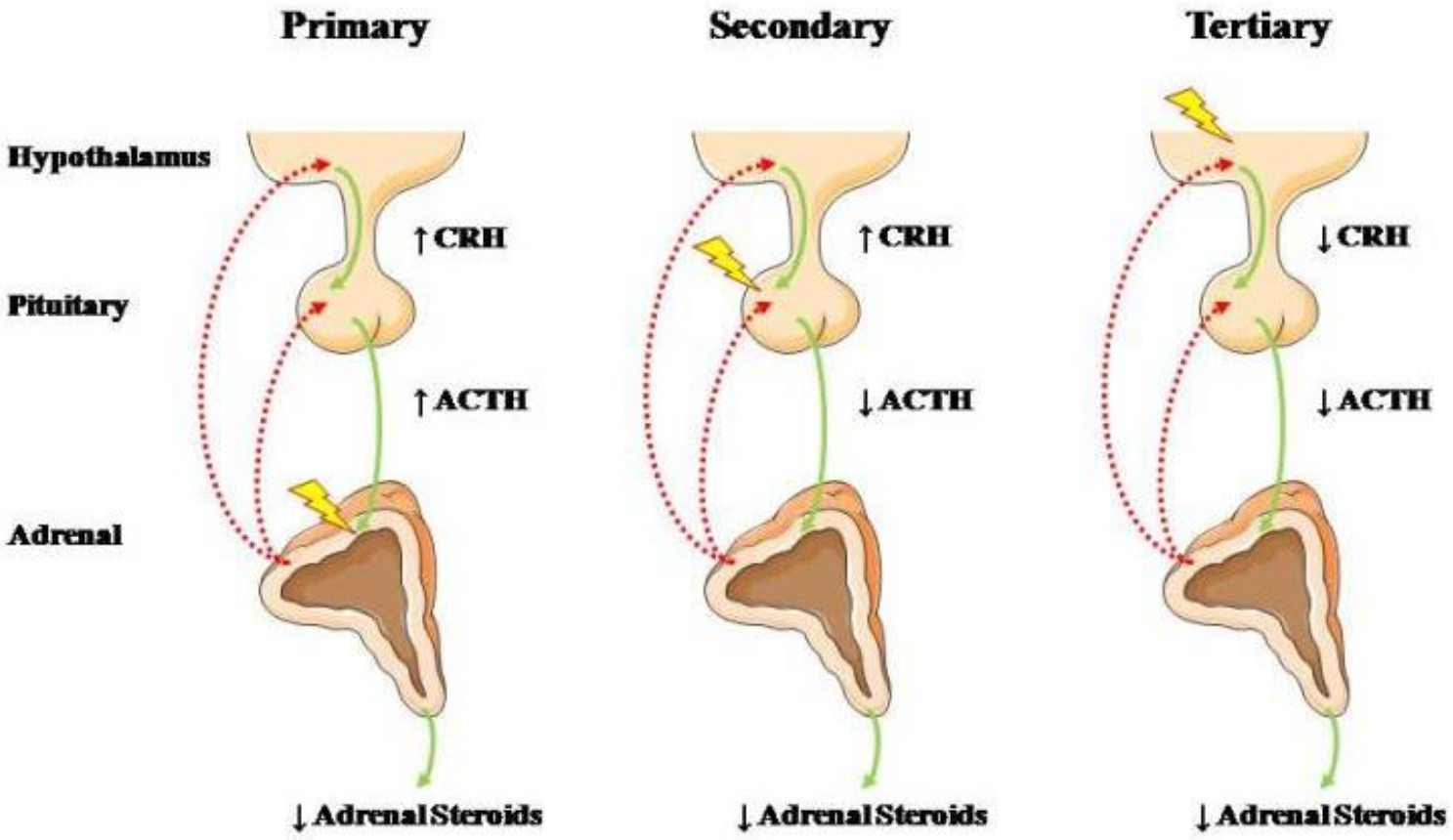
- **Secondary adrenal insufficiency:**

is caused by impairment of the pituitary gland or hypothalamus.



- **Tertiary adrenal insufficiency:**

is due to hypothalamic disease and decrease in corticotropin releasing factor (CRF).


Primary
Secondary
Tertiary
Hypothalamus
Pituitary
Adrenal
↑CRH
↑ACTH
↓Adrenal Steroids
↑CRH
↓ACTH
↓Adrenal Steroids
↓CRH
↓ACTH
↓Adrenal Steroids

Addison's disease

Adrenal glands
not produce
sufficient steroid
hormones

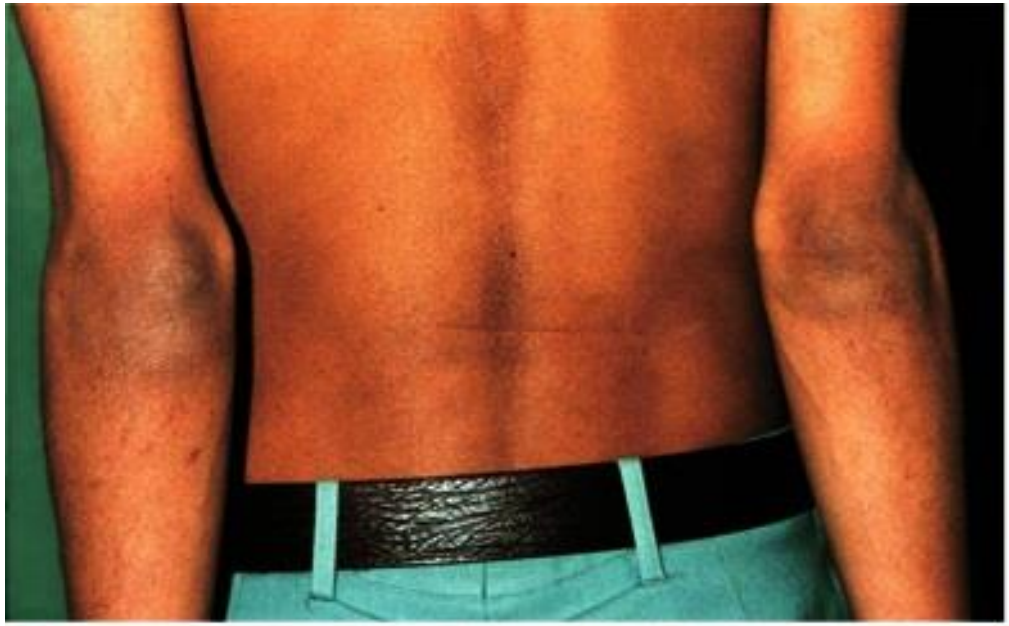
Skin
Hyperpigmentation

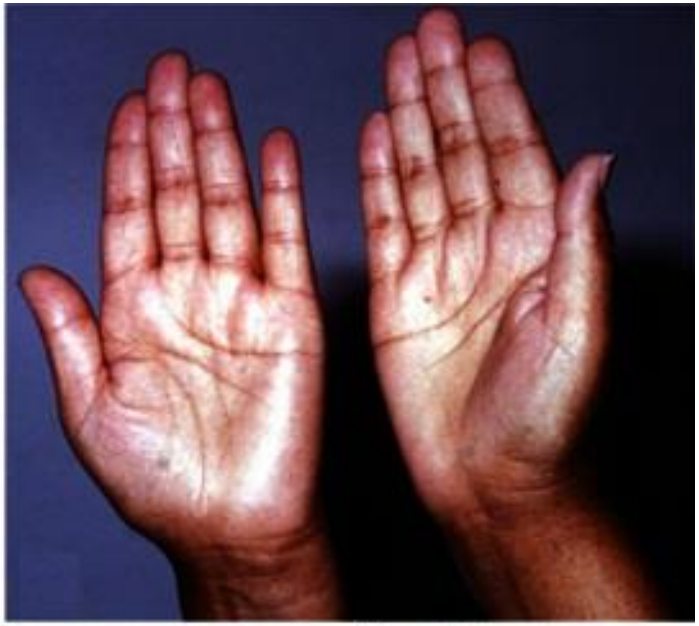
Low blood pressure
Weakness
Weight loss

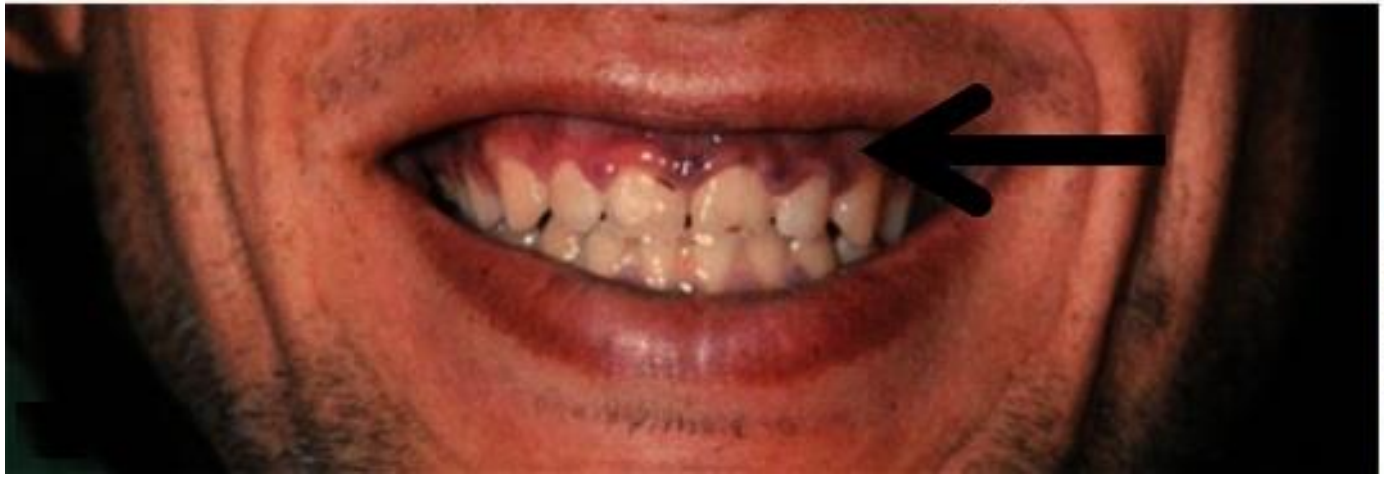
Gastrointestinal
Nausea
Diarrhea
Vomiting
Constipation
Abdominal pain

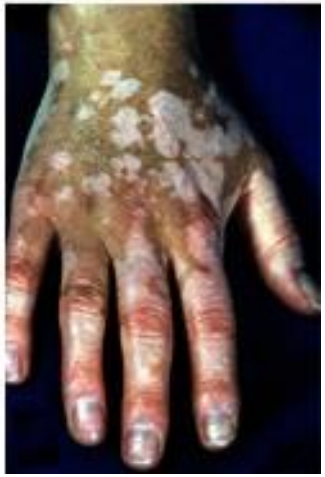
Skin
Vitiligo

Adrenal crisis:
- fever;
- syncope;
- convulsions;
- hypoglycemia;
- hyponatremia;
- severe vomiting and diarrhea.



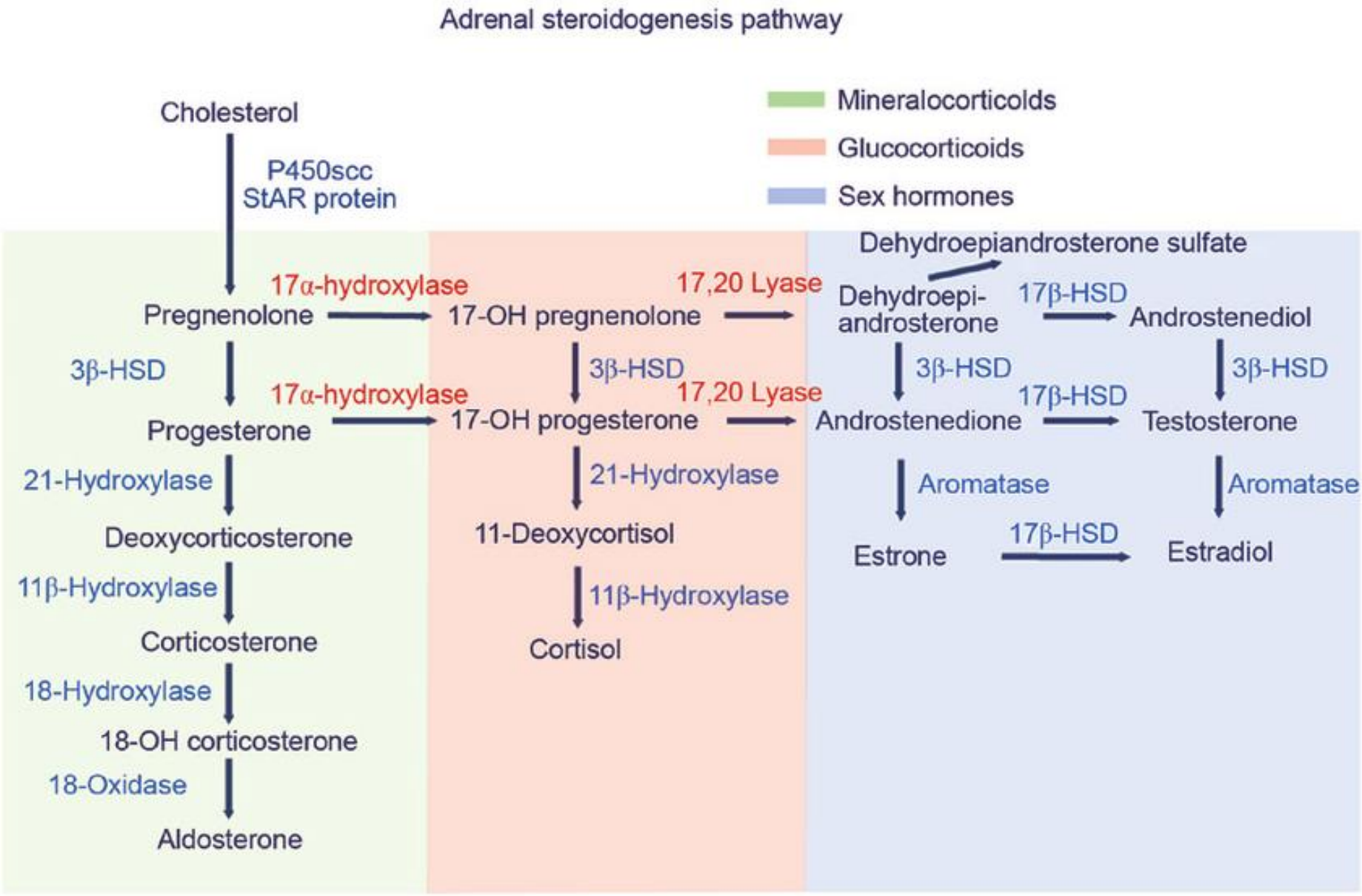






Adrenal androgens

- Several moderately active male sex hormones, most important: dehydroepiandrosterone. (mainly secreted during fetal life)
- Also progesterone and estrogen (female sex hormones), are secreted in minute quantities.
- Weak effects in humans; part of the early development of the male sex organs. Mild effects in the female throughout life (pubic and axillary hair)
- In extra-adrenal tissue, some of these hormones are converted into testosterone; the primary male sex hormone.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17-OH progesterone
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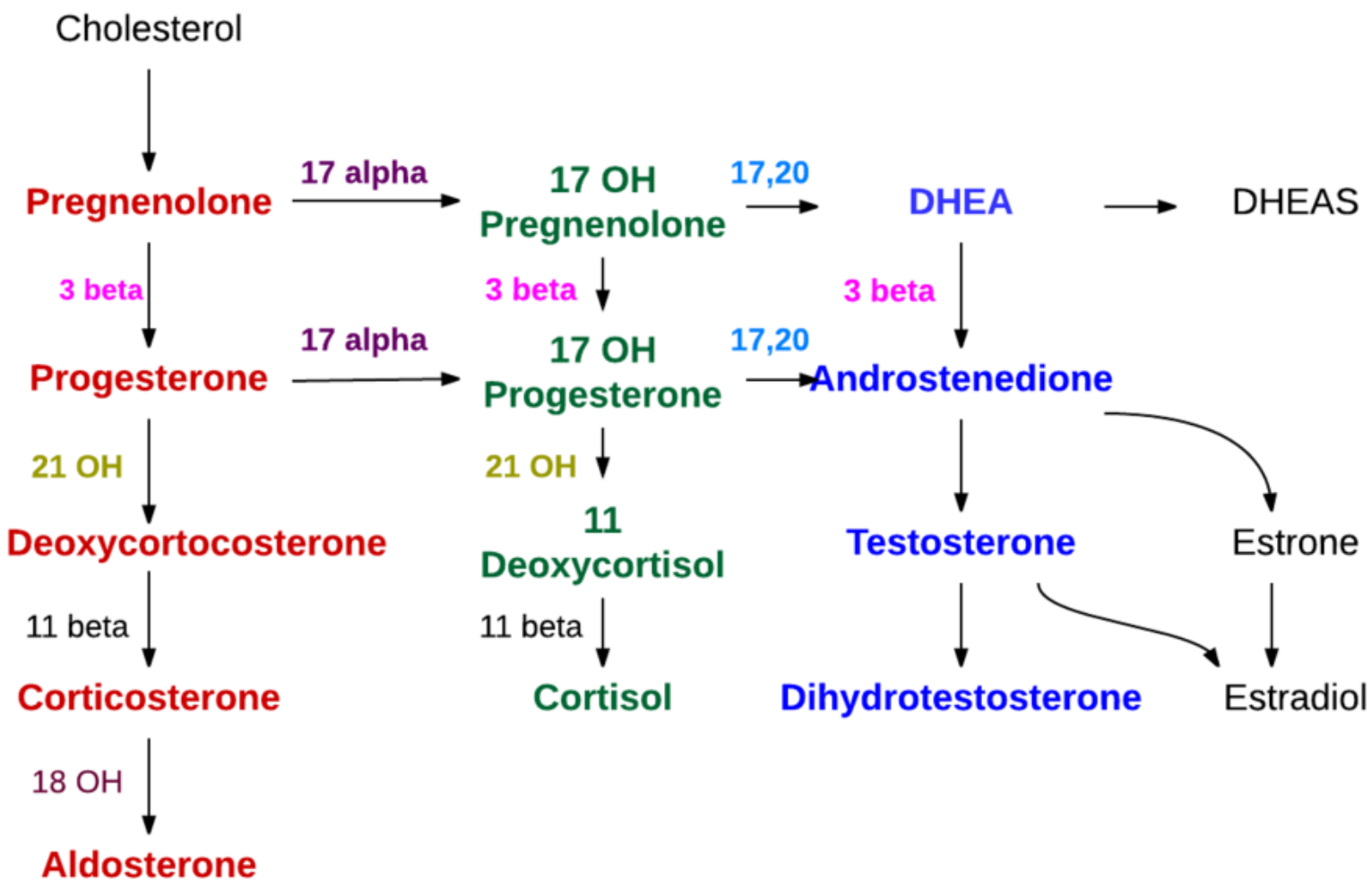
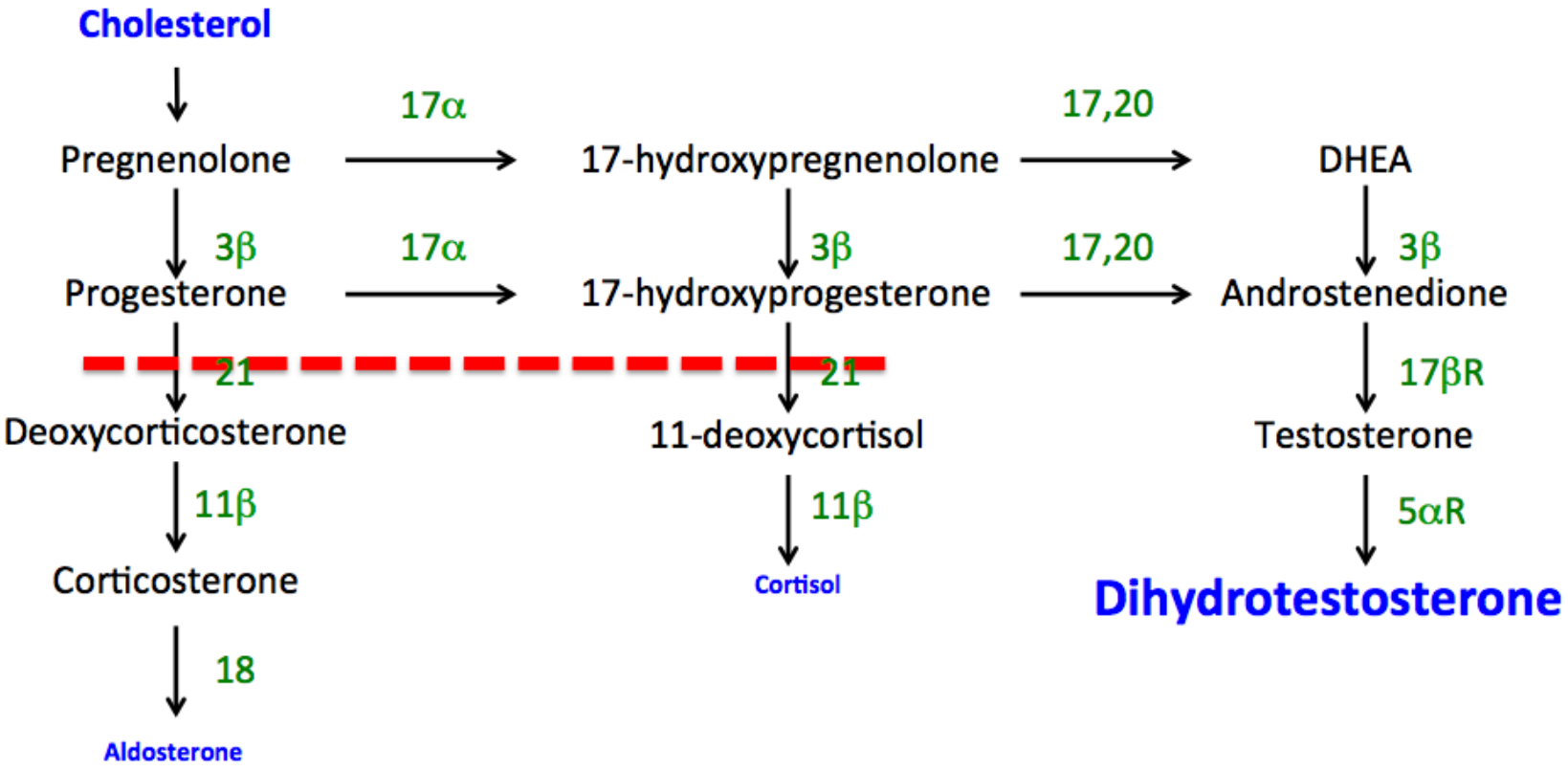
Androstenedione
17β-HSD
Testosterone
21-Hydroxylase
21-Hydroxylase
Aromatase
Aromatase
Deoxycorticosterone
11-Deoxycortisol
Estrone
17β-HSD
Estradiol
11β-Hydroxylase
11β-Hydroxylase
Corticosterone
Cortisol
18-Hydroxylase
18-OH corticosterone
18-Oxidase
Aldosterone

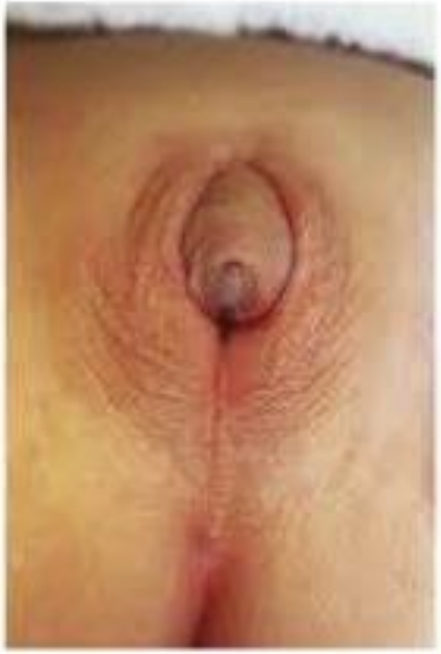

Cholesterol
Pregnenolone
17 alpha
17 OH Pregnenolone
17,20
DHEA
DHEAS
3 beta
3 beta
3 beta
Progesterone
17 alpha
17 OH Progesterone
17,20
Androstenedione
21 OH
21 OH
Deoxycortocosterone
11 Deoxycortisol
Testosterone
Estrone
11 beta
11 beta
Corticosterone
Cortisol
Dihydrotestosterone
Estradiol
18 OH
Aldosterone

21 hydroxylase deficiency

- Impairs synthesis of cortisol and aldosterone
- ↓ Cortisol and ↑ ACTH secretion → adrenal gland hyperplasia
- Some of the accumulated precursors are diverted to the biosynthesis of sex hormones → signs of androgen excess
- In severe cases,mineralocorticoid deficiency is evident → salt and water loss → hypovolemic shock
- Late presentation in adult life


Cholesterol
Pregnenolone
17α
17-hydroxypregnenolone
17,20
DHEA
3β
Progesterone
17α
17-hydroxyprogesterone
3β
17,20
Androstenedione
3β
21
21
17βR
Deoxycorticosterone
11-deoxycortisol
Testosterone
11β
11β
5αR
Corticosterone
Cortisol
Dihydrotestosterone
18
Aldosterone

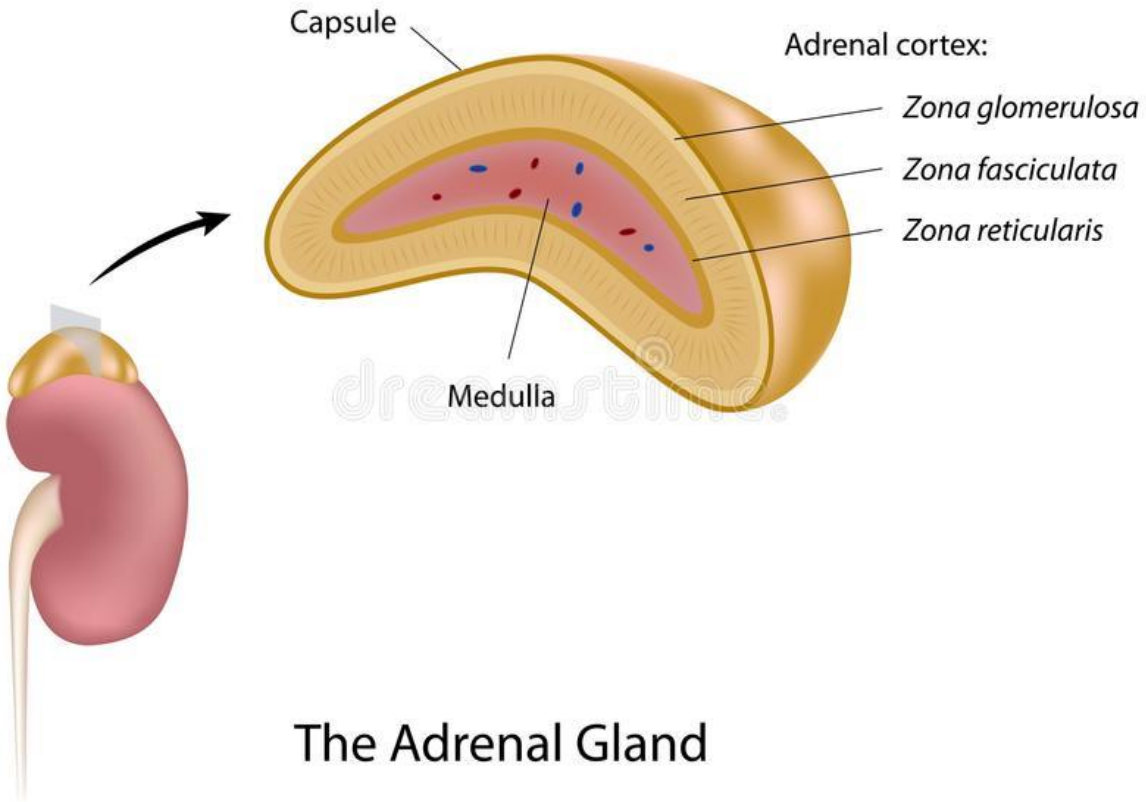
Ambiguous genitalia



True or false

1. Adrenal cortex is stimulated by CRH
2. There are 3 layers of cells in adrenal medulla
3. Cortisol is a steroid hormone
4. Cortisol causes protein catabolism in liver
5. Cortisol will increase glycogenolysis
6. Aldosterone is produced from Cholesterol
7. Renin is high in primary hyperaldosteronism

Adrenal medulla



Adrenal medulla

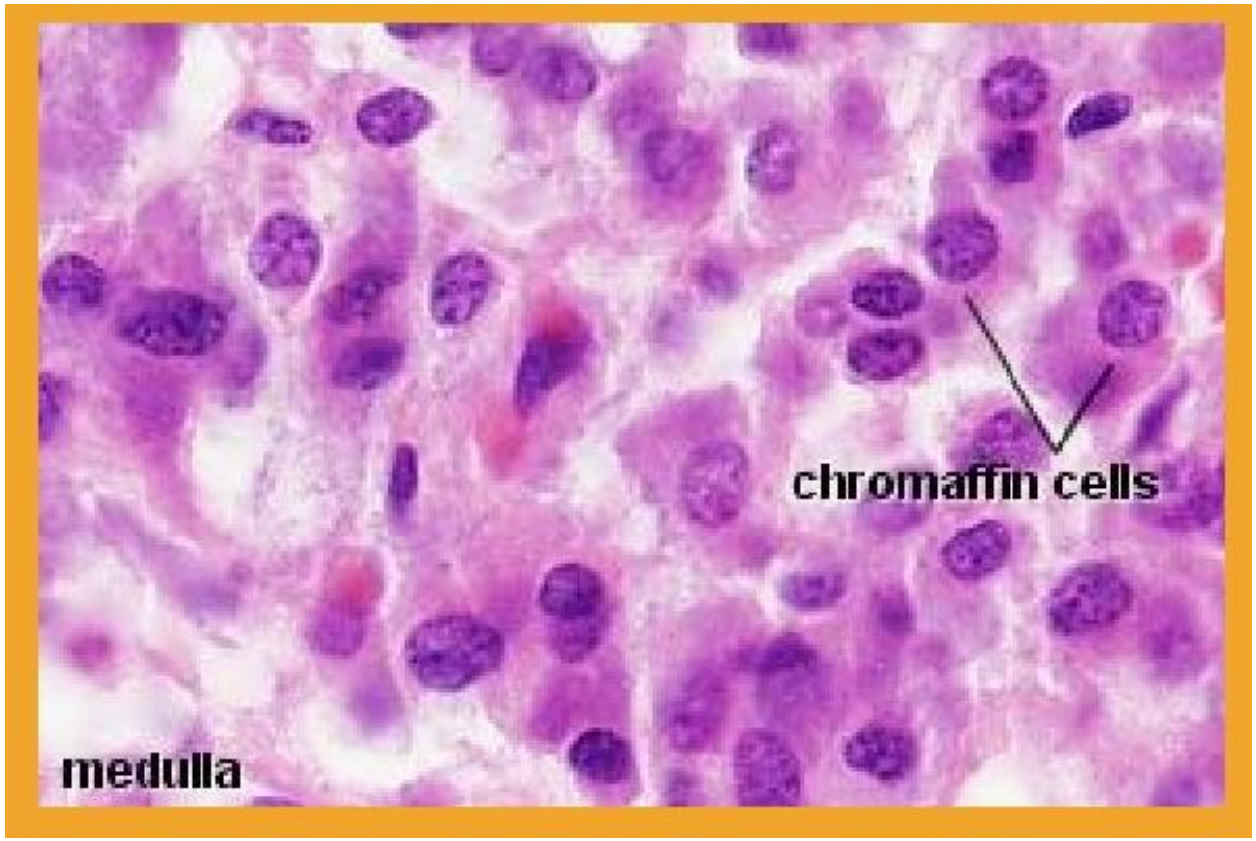
- Chromaffin cells produce epinephrine (or adrenaline), a catecholamine that is synthesized from the amino acid tyrosine.

- Although the primary product of the medulla is epinephrine, it also produces variable amounts of the epinephrine precursor norepinephrine.

Adrenal Medulla

- Adrenal medulla bridges the endocrine and sympathetic nervous systems
- Cells of the medulla, termed chromaffin cells because the catecholamines that they contain stain avidly with chromium salts, derive from neural crest cells
- The adrenomedullary cells synthesize and secrete epinephrine and—to a lesser extent—norepinephrine
- Norepinephrine is the neurotransmitter of the sympathetic division of the autonomic nervous system

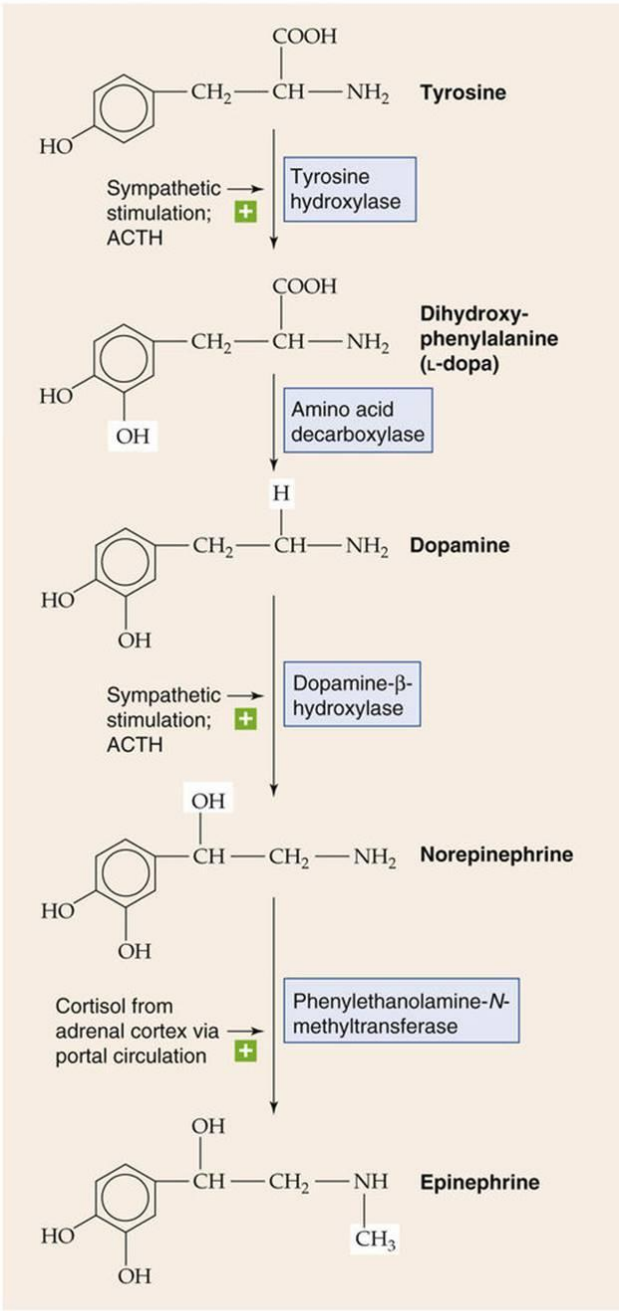
Chromaffin cells

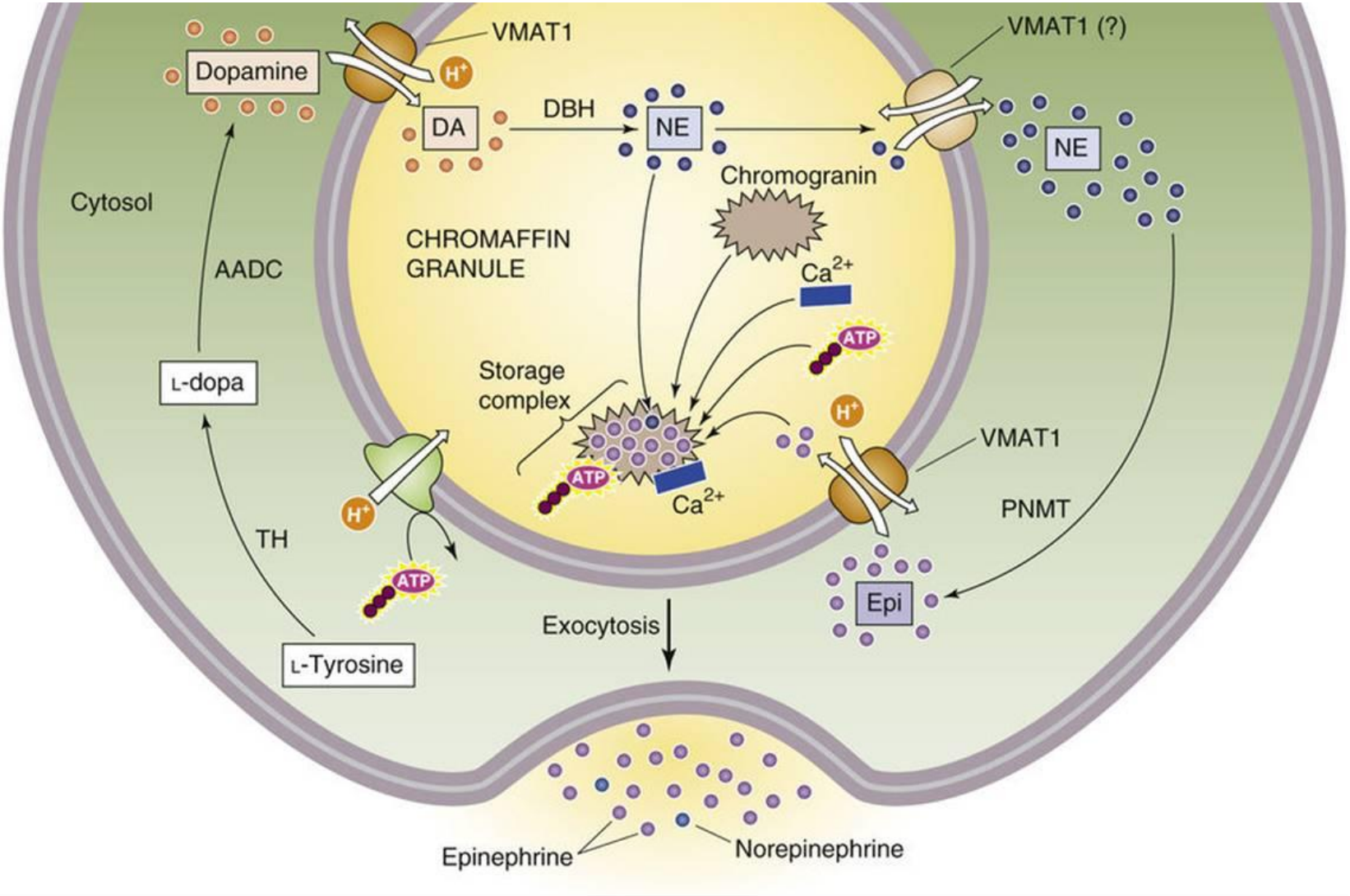


Adrenal Medulla

- Chromaffin cells are the structural and functional equivalents of the postganglionic neurons in the sympathetic nervous system
- The preganglionic sympathetic fibers of the splanchnic nerves, which release acetylcholine (ACh), are the principal regulators of adrenomedullary hormone secretion
- Only chromaffin cells of the adrenal medulla have the enzyme for epinephrine synthesis

A CATECHOLAMINE SYNTHESIS




VMAT1
VMAT1 (?)
Dopamine
H+
DA
DBH
NE
NE
Chromogranin
Cytosol
CHROMAFFIN
GRANULE
AADC
Ca2+
ATP
L-dopa
Storage
complex
H+
VMAT1
ATP
Ca2+
PNMT
TH
H+
ATP
Epi
Exocytosis
L-Tyrosine
Epinephrine
Norepinephrine

Epinephrine synthesis

- Epinephrine synthesis is under the control of the CRH-ACTH-cortisol axis at two levels

- First, ACTH stimulates the synthesis of L-dopa and norepinephrine

- Second, cortisol transported from the adrenal cortex by the portal circulation to the medulla upregulates Phenylethanolamine N-methyltransferase (PNMT) in chromaffin cells
- The result is synergy between the CRH-ACTH-cortisol axis and the sympathetic-epinephrine axis.
- Thus, the stress that is sensed and propagated by the CRH-ACTH-cortisol axis sustains the epinephrine response.

Epinephrine

- Secretory granules of the adrenal medulla contain very high concentrations of catecholamines
- Catecholamines—along with ATP and Ca2+—bind to granular proteins called chromogranins and thus are not osmotically active in these storage vesicles
- Chromogranins are what make dense-core vesicles dense.
- In humans, the dominant chromogranin is chromogranin B.

Regulation of secretion

- The release of catecholamines is initiated by CNS control.
- ACh released from preganglionic neurons in the splanchnic nerves acts on nicotinic ACh receptors to depolarize the postganglionic chromaffin cells.
- This depolarization triggers the opening of voltage-gated Ca2+ channels, a process that raises [Ca2+] and triggers the exocytotic release of epinephrine.
- The release of chromogranin A has been used as a marker of adrenal medullary activity

Actions

- Biological actions of catecholamines are very brief, lasting only ~10 seconds in the case of epinephrine
- Fight-or-flight response to stress
- Increases in heart rate and contractility, mobilization of fuel stores from muscle and fat, piloerection, pupillary dilatation, and increased sphincter tone of the bowel and bladder

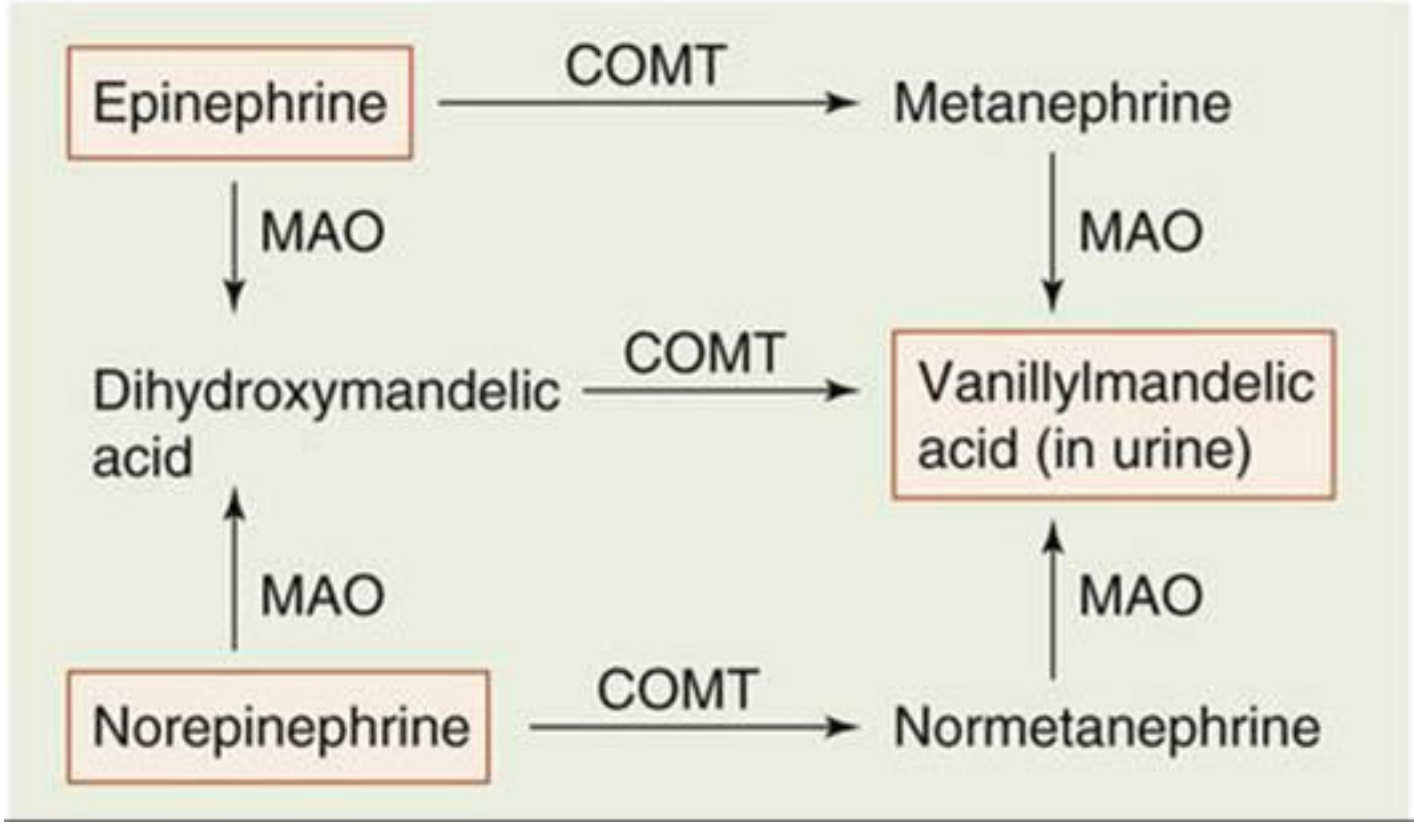
Degredation

- Circulating catecholamines are degraded first by the enzyme catechol-O-methyltransferase (COMT), which is present in high concentrations in endothelial cells and the heart, liver, and kidneys

- COMT converts epinephrine to metanephrine, as well as norepinephrine to normetanephrine

- A second enzyme, monoamine oxidase, converts these metabolites to vanillylmandelic acid (VMA)

B DEGRADATIVE METABOLISM OF CATECHOLAMINES

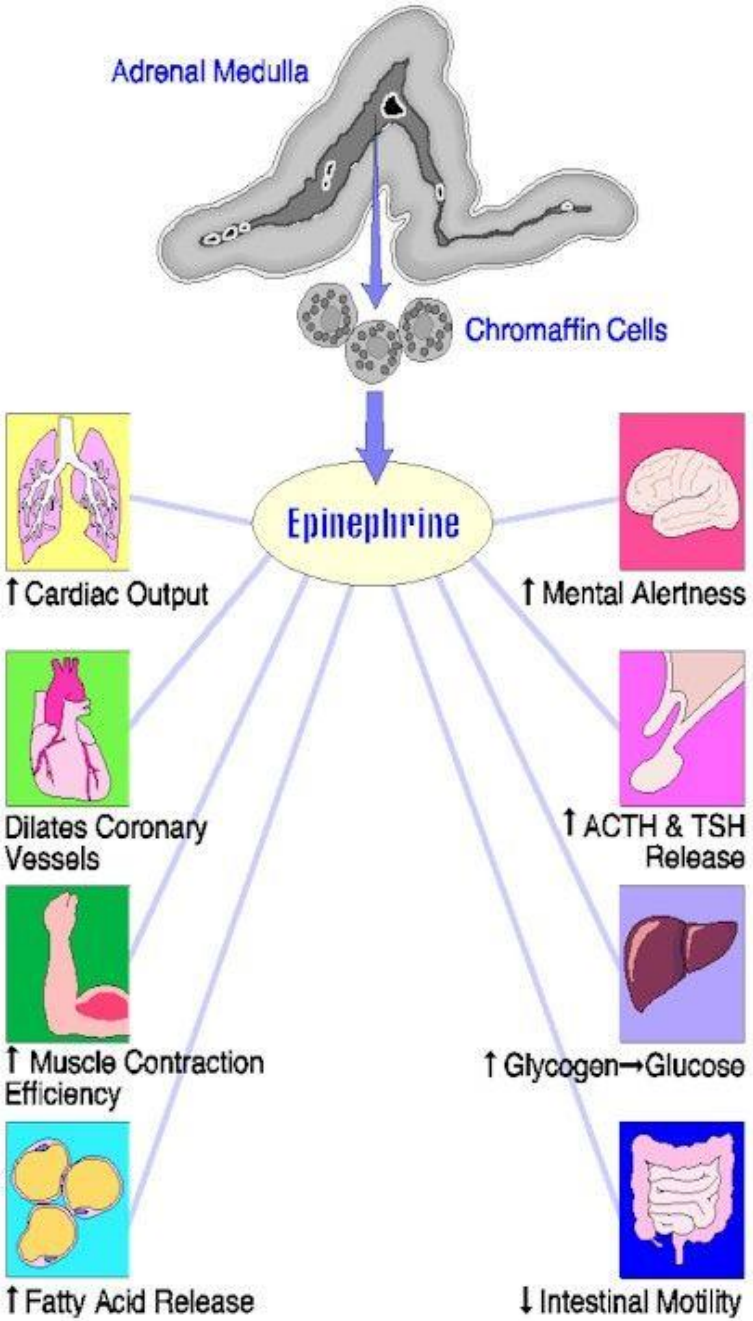


- Determination of the concentration of catecholamines, metanephrines, and VMA in the urine provides a measure of the total adrenal catecholamine production by both the adrenal medulla and the sympathetic system.

Actions

- Catecholamines bind to α and β adrenoceptors on the cell surface and act through heterotrimeric G proteins
- Epinephrine and norepinephrine can each bind to more than one type of adrenergic receptor, or adrenoceptor

	α_1	α_2	β_1	β_2
Blood vessels	constrict	constrict		dilate
Bronchi	constrict			agonists used in asthma to dilate the bronchi relax
Heart			↑ Rate and contraction	↑ Rate and contraction
Nerve endings		negative feedback receptors ↓ NE release	↑ NE release	↑ NE release
Mast cells				↓ Hist. release
2nd Messenger	IP_3, DAG	↓ cAMP	↑ cAMP	↑ cAMP

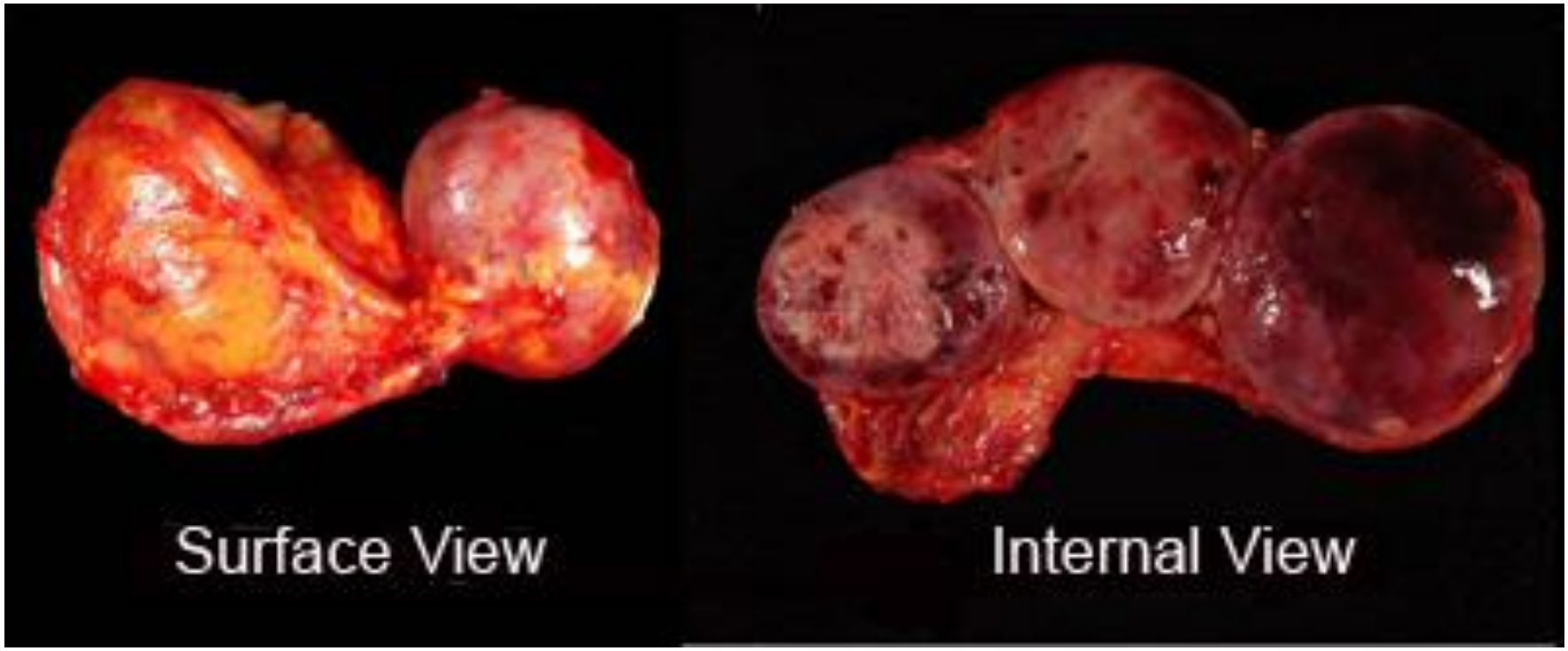

Adrenal Medulla
Chromaffin Cells
Epinephrine
↑ Cardiac Output
↑ Mental Alertness
Dilates Coronary Vessels
↑ ACTH & TSH Release
↑ Muscle Contraction Efficiency
↑ Glycogen→Glucose
↑ Fatty Acid Release
↓ Intestinal Motility

Pheochromocytoma

- A pheochromocytoma is a relatively uncommon tumor caused by hyperplasia or more rarely neoplasia of either adrenal medullary tissue or extra-adrenal chromaffin tissue that failed to involute after birth
- make catecholamines, just like the normal medulla, except in an unregulated fashion.
- Paroxysmal (sudden) hypertension, tachycardia, headache, episodes of sweating, anxiousness, tremor, and glucose intolerance usually dominate the clinical findings.

Clinical Features

Headaches
Sweating attacks
Palpitations and tachycardia
Hypertension, sustained or paroxysmal
Anxiety and panic attacks
Pallor
Nausea
Abdominal pain
Weakness
Weight loss
Paradoxical response to antihypertensive drugs
Polyuria and polydipsia
Constipation
Orthostatic hypotension
Dilated cardiomyopathy
Erythrocytosis
Elevated blood sugar
Hypercalcemia


Surface View
Internal View

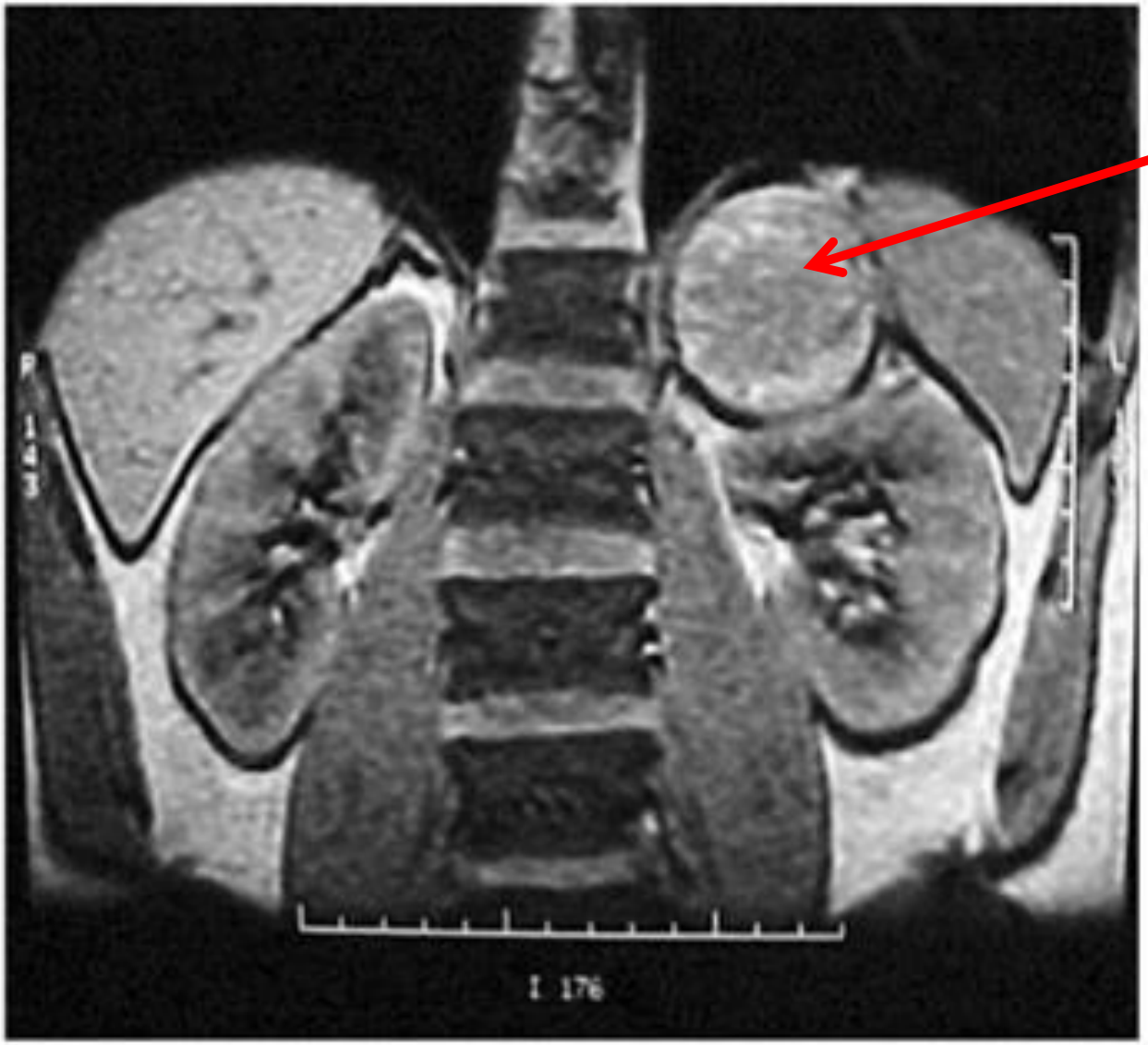


***Figure 2** – MRI showing large adrenal mass - hypersignal in T2.*

True or false

1. Epinephrine is synthesized from tyrosine
2. Epinephrine synthesis is under the control of the CRH-ACTH-cortisol axis
3. Chromaffin cells of adrenal medulla produce epinephrine
4. COMT converts epinephrine to metanephrine
5. Paroxysmal symptoms are a feature of phaeochromoctoma
6. Only chromaffin cells of the adrenal medulla have the enzyme for epinephrine synthesis


Stress
Relax